

No. 23-1540

**In the United States Court of Appeals
for the Federal Circuit**

AZURITY PHARMACEUTICALS, INC.,

Plaintiff-Appellant,

v.

ALKEM LABORATORIES LTD,

Defendant-Appellee.

*Appeal from the United States District Court for the District of Delaware
Case No. 1:19-cv-02100, Judge Mitchell S. Goldberg*

JOINT APPENDIX

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TABLE OF CONTENTS

	Page
Docket No. 214 – Order	Appx1
Docket No. 213 – Memorandum Opinion	Appx2
Docket No. 216 – Notice of Appeal, filed by Azurity	Appx53
Docket Sheet for Case No. 1:19-cv-02100	Appx56
U.S. Patent No. 10,786,482 (PTX-1, Admitted into evidence on 8/16/22)	Appx81
U.S. Patent No. 10,918,621 (PTX-2, Admitted into evidence on 8/16/22)	Appx108
Docket No. 39 – Azurity’s First Amended Complaint	Appx136
Docket No. 41 – Alkem’s Answer to First Amended Complaint .	Appx153
Docket No. 72 – Joint Claim Construction Brief (Sealed).....	Appx176
Docket No. 73 – Appendix in support of Joint Claim Construction Brief, with Exhibits A-C.....	Appx237
Docket No. 79 – August 23, 2021 Claim Construction Hearing Transcript	Appx761
Docket No. 97 – Memorandum Opinion re Claim Construction .	Appx814
Docket No. 98 – Order re Claim Construction	Appx829
Docket No. 101 – Stipulation and [Proposed] Order to Stay Pending Appeal.....	Appx830
Docket No. 182-1 – Proposed Pretrial Order, Exhibit 3	Appx832

Docket No. 184 – July 29, 2022 Pretrial Hearing Transcript	Appx946
Docket No. 185 – Amended Exhibit 1, Plaintiff’s and Defendant’s Joint Statement of Uncontested Facts (Sealed)	Appx974
Docket No. 194 – Transcript of Trial Proceedings [1-236] held on August 16, 2022, before Judge Goldberg	Appx984
Docket No. 195 – Transcript of Trial Proceedings [237-473], held on August 17, 2022, before Judge Goldberg	Appx1250
Docket No. 196 – Transcript of Trial Proceedings [474-571], held on August 18, 2022, before Judge Goldberg	Appx1520
Docket No. 197 – Azurity’s Post Trial Brief (Sealed)	Appx1632
Docket No. 198 – Alkem’s Post Trial Brief (Sealed)	Appx1679
Docket No. 204 – Order re Supplemental Briefs	Appx1727
Docket No. 205 – Azurity’s Supplemental Post Trial Brief (Sealed)	Appx1729
Docket No. 206 – Alkem’s Supplemental Post Trial Brief (Sealed)	Appx1757
Docket No. 207 – Alkem’s Declaration in support of Supplemental Post Trial Brief, with Exhibits A-E (Sealed)	Appx1769
Docket No. 212 – January 19, 2023 Oral Argument Hearing Transcript	Appx2015
DTX-1005, Admitted into evidence on 8/17/22	Appx2111
DTX-1010, Admitted into evidence on 8/16/22	Appx2146
DTX-1033, Admitted into evidence on 8/17/22	Appx2155

DTX-1034, Admitted into evidence on 8/17/22	Appx2174
DTX-1057, Admitted into evidence on 8/16/22	Appx2175
DTX-1067, Admitted into evidence on 8/17/22	Appx2189
DTX-1073, Admitted into evidence on 8/16/22	Appx2208
DTX-1074, Admitted into evidence on 8/17/22	Appx2225
DTX-1077, Admitted into evidence on 8/17/22	Appx2231
DTX-1078, Admitted into evidence on 8/17/22	Appx2238
DTX-1081, Admitted into evidence on 8/17/22	Appx2241
DTX-1082, Admitted into evidence on 8/17/22	Appx2249
DTX-1083, Admitted into evidence on 8/17/22	Appx2256
DTX-1094, Admitted into evidence on 8/16/22	Appx2267
DTX-1109, Admitted into evidence on 8/17/22	Appx2290
DTX-1118, Admitted into evidence on 8/17/22	Appx2315
DTX-1144, Admitted into evidence on 8/16/22	Appx2322
PTX-38, Admitted into evidence on 8/17/22.....	Appx2332
PTX-41, Admitted into evidence on 8/17/22.....	Appx2335
PTX-50, Admitted into evidence on 8/16/22.....	Appx2342
PTX-52, Admitted into evidence on 8/16/22.....	Appx2349
PTX-55, Admitted into evidence on 8/16/22.....	Appx2443

PTX-60, Admitted into evidence on 8/16/22.....	Appx2509
PTX-67, Admitted into evidence on 8/16/22.....	Appx2659
PTX-69, Admitted into evidence on 8/16/22.....	Appx2690
PTX-73, Admitted into evidence on 8/16/22.....	Appx2708
PTX-78, Admitted into evidence on 8/17/22.....	Appx2726
PTX-82, Admitted into evidence on 8/17/22.....	Appx2734
PTX-105, Admitted into evidence on 8/17/22.....	Appx2740
PTX-113, Admitted into evidence on 8/17/22.....	Appx2788
PTX-114, Admitted into evidence on 8/17/22.....	Appx2832
PTX-119, Admitted into evidence on 8/17/22.....	Appx2843
PTX-125, Admitted into evidence on 8/17/22.....	Appx2856
PTX-137, Admitted into evidence on 8/17/22.....	Appx2864
PTX-144, Admitted into evidence on 8/17/22.....	Appx2890
PTX-146, Admitted into evidence on 8/17/22.....	Appx2901
PTX-149, Admitted into evidence on 8/17/22.....	Appx2909
PTX-164, Admitted into evidence on 8/17/22.....	Appx2916
DDX-019, Admitted into evidence on 8/17/22.....	Appx2926
DDX-020, Admitted into evidence on 8/17/22.....	Appx2927
DDX-021, Admitted into evidence on 8/17/22.....	Appx2928

DDX-022, Admitted into evidence on 8/17/22.....	Appx2929
DDX-023, Admitted into evidence on 8/17/22.....	Appx2930
Deposition Designations of G. Mosher, submitted at trial.....	Appx2931
U.S. Patent No. 9,669,008.....	Appx3073
Docket No. 189 – August 29, 2022 Letter to Judge Goldberg (SEALED).....	Appx3099
Docket No. 190 – August 30, 2022 Letter to Judge Goldberg (SEALED).....	Appx3108
Docket No. 191 – Order.....	Appx3110

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

AZURITY PHARMACEUTICALS, INC.,

Plaintiff,

v.

ALKEM LABORATORIES LTD.,

Defendant.

Civil Action

No. 19-cv-2100

ORDER

AND NOW, this 10th day of February, 2023, following a bench trial held on August 16, 17, and 18, 2022, and for the reasons set forth in the accompanying memorandum opinion, it is hereby **ORDERED** that **JUDGMENT** is entered in favor of Defendant and against Plaintiff on Counts VI and VII of Plaintiff's Amended Complaint.

BY THE COURT:

/s/ Mitchell S. Goldberg
MITCHELL S. GOLDBERG, J.

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

AZURITY PHARMACEUTICALS, INC.,

Plaintiff,

v.

ALKEM LABORATORIES LTD.,

Defendant.

Civil Action

No. 19-cv-2100

MEMORANDUM OPINION

Goldberg, J.¹

February 10, 2023

This lawsuit was brought under the Hatch Waxman Act for patent infringement pursuant to 35 U.S.C. § 271(e)(2)(a). Plaintiff Azurity Pharmaceuticals, Inc. (“Azurity”) claims that an Abbreviated New Drug Application (ANDA) submitted by Defendant Alkem Laboratories Ltd. (“Alkem”) infringes U.S. Patent Nos. 10,786,482 (the ’482 patent) and 10,918,621 (the ’621 patent), both titled “Enalapril formulations.” Azurity asserts claims 16, 18, 22, 23, and 28 of the ’482 patent and claims 4, 7, 17, and 18 of the ’621 patent. Alkem denies infringement and alleges that the patents in suit are invalid due to obviousness and insufficient written description.

After presiding over a three-day bench trial, I find that Azurity has established by a preponderance of the evidence that Alkem’s ANDA infringes all asserted claims. However, I also conclude that Alkem has presented clear and convincing evidence that those claims are invalid for obviousness and lack of written description. This opinion sets forth my reasons in reaching these verdicts.

¹ Pursuant to 28 U.S.C. § 292(b), I have been designated to serve as a visiting judge for the District of Delaware to handle this matter and other District of Delaware cases.

I. BACKGROUND

The patents in suit claim liquids containing the blood pressure medicine enalapril. Azurity did not invent enalapril, which had existed for decades preceding Azurity's invention. Azurity claims to have invented a way to mix enalapril with water and prevent the mixture from degrading over a period of 12 to 24 months. Alkem's ANDA is also a mixture of enalapril in water that does not degrade over 24 months.

Alkem concedes that its ANDA infringes most asserted claim limitations, disputing only two. First, Alkem contends that its ANDA does not infringe because it contains an ingredient that is not recited in any asserted claim: a "pH adjuster" added to ensure that the pH of the mixture is within a target range. According to Alkem, because none of the asserted claims recite pH adjusters, the presence of these ingredients precludes infringement of those claims that are partially closed to unlisted ingredients. Azurity responds that pH adjusters are optional in Alkem's ANDA and therefore do not affect the infringement analysis. Alternatively, Azurity argues that when a pH adjuster is added, it disappears by reacting with other ingredients in the mixture such that it is no longer present in the final liquid, thus defeating Alkem's noninfringement argument.

Alkem also contends that Azurity failed to prove that the concentration of the buffer in Alkem's ANDA is within the claimed range, again relying on the pH adjusters in conjunction with testimony from Azurity's expert Dr. Little, who opined that the pH adjusters react with citric acid to form components of the buffer. Alkem reasons that if Dr. Little's testimony is credited, the reaction he described must produce some unknown quantity of buffer, meaning there is a failure of proof that the amount of buffer left after the reaction is within the claimed range.

On the issue of validity, Alkem alleges that the asserted patent claims would have been obvious in light of the prior art and that the claims are inadequately described by the patents' written

specification. More specifically, Alkem alleges that it would have been obvious to a person of ordinary skill in the art (a POSA) to make an enalapril liquid as set out in the claims: (1) using each claimed ingredient; (2) in the claimed amounts; (3) with no other ingredients that “materially affect the basic and novel properties of the invention”; and (4) meeting the two limitations regarding the liquid being “stable” and having at least 95% enalapril with no more than 5% impurities at the end of the storage period. (See, e.g., ’621 patent, Claim 4.)

While Azurity did not concede that any aspect of its invention was obvious, at trial Azurity did not dispute that the individual claimed ingredients—enalapril, water, citrate buffers, paraben preservatives, sweeteners, and flavors—were known prior to its invention. Instead, the focus of the parties’ dispute is whether it would have been obvious how to combine those ingredients into a liquid that would be stable for as long as the claims require—12 to 24 months. As set forth in greater detail below, the parties offered prior studies on the tendency of enalapril to degrade in water and presented conflicting views as to what a POSA would glean from those studies about the possibility of keeping enalapril stable for 12 to 24 months.

Regarding written description, the issue is whether the patents’ specification adequately describes stable enalapril liquids that contain paraben preservatives. Alkem asserts that although the specification states that parabens can be used as a preservative, it does not say which liquids containing parabens will be stable for 12 to 24 months.

II. INFRINGEMENT

A. Facts Relevant to Infringement

1. Expert Testimony

The parties stipulated that all experts were qualified, and, indeed, the background and experience of each expert was impressive. Briefly summarized, Azurity's witness Dr. Stephen Little is an expert in pharmaceutical formulation who has undergraduate and doctoral degrees in chemical engineering and has founded multiple companies engaged in pharmaceutical formulation. (N.T. 93-97.) Azurity's witness Dr. John Mahan is an expert in the treatment of young children with hypertension who holds various teaching, research, and leadership roles in pediatric nephrology. (N.T. 387-90.) Alkem's witness Dr. Barrett Rabinow is also an expert in pharmaceutical formulation who has undergraduate and doctoral degrees in chemistry and spent over 39 years as a chemist working on pharmaceutical formulations. (N.T. 177-85.) Finally, Alkem's witness Dr. Panayiotis Constantinides, also an expert in pharmaceutical formulation, has degrees in chemistry and biochemistry and has developed pharmaceutical formulations over a period of 35 years. (N.T. 244-50.)²

2. Asserted Claims

Azurity asserts claims 16, 18, 22, 23, and 28 of the '482 patent and claims 4, 7, 17, and 18 of the '621 patent. Claim 4 of the '621 patent is illustrative, and reads:

A stable oral liquid formulation, consisting essentially of:

- (i) about 0.6 to about 1.2 mg/mL enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;

² These experts also offered testimony relevant to validity.

- (iii) a preservative, wherein the preservative is a paraben or a mixture of parabens; and
- (iv) water;

wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;

wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$. for at least 12 months; []

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period[]; and]

wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.

(’621 patent, Claim 4 (independent claims inserted).)³

3. Alkem’s Accused Product

Alkem’s accused product is an abbreviated new drug application (ANDA) for an enalapril liquid. It is undisputed that Alkem’s ANDA contains many of the same ingredients in the same amounts as the asserted claims require, including the same active ingredient, preservative, water, and sweetener. (Amended Undisputed Facts ¶¶ 38-48; N.T. 115-16 (Little).) It is also undisputed that Alkem’s ANDA meets the pH and stability limitations of all asserted claims, and that it meets the limitation of claim 18 of the ’482 patent that the formulation not contain mannitol. (N.T. 118-23 (Little).)

But for two reasons, Alkem does not concede infringement. First, Alkem points to the fact that its ANDA states that pH adjusters—sodium hydroxide and hydrochloric acid—should be added in an amount “q.s.” The term “q.s.” means “quantum satis” or “the quantity that’s necessary.” (N.T. 138 (Little).) Thus, sodium hydroxide and hydrochloric acid will be added as necessary to Alkem’s ANDA to achieve the target pH range. (N.T. 141, 172 (Little).) Alkem’s ANDA does

³ The parties stipulated that “no terms of the patents-in-suit require construction” and thus no hearing on claim construction was held. (ECF No. 84.)

not explicitly say whether the target pH range can be achieved without adding pH adjusters. (N.T. 173-74 (Little).) The ANDA describes “exhibit batches” of the formulation, all of which required the addition of sodium hydroxide to meet the target pH range. (N.T. 139-40, 151-52, 158-59, 164 (Little).)

The patents in suit do not claim pH adjusters, and, for that reason, Alkem argues that its ANDA does not infringe certain asserted claims. In response, Azurity’s expert Dr. Little testified that sodium hydroxide (the pH adjuster) “dissociates” or splits apart in water. (N.T. 140 (Little).) In addition, when sodium hydroxide is added to the citrate buffer present in Alkem’s ANDA, it reacts with citric acid. (N.T. 140-43 (Little).) For either of these two reasons, Azurity maintains that the pH adjusters are no longer present after Alkem’s ANDA solution is mixed, meaning that their addition does not preclude infringement.

Alkem’s second reason for asserting that its ANDA does not infringe is that Azurity has not proven that its ANDA has a buffer in the same concentration that the claims require. Alkem’s ANDA specifies that a buffer should be added that consists of 1.820 mg/mL (milligrams per milliliter) of citric acid and 0.150 mg/mL of sodium citrate. (N.T. 116 (Little).) Dr. Little testified that when these numbers are converted from mg/mL to molar concentration and added together, the total is between 5 mM (“millimolar”) and 20 mM, which matches the asserted claims. (N.T. 117 (Little).) But for reasons explained in more detail below, Alkem disputes that this computation shows that the buffer concentration limitation is met. Alkem points to the reaction between sodium hydroxide and citric acid Dr. Little testified to, and argues that the products of this reaction must affect the buffer concentration in some unknown way. Alkem did not offer testimony to support this argument.

B. Discussion

It is an act of patent infringement to “submit . . . an application under . . . the Federal Food, Drug, and Cosmetic Act . . . for a drug claimed in a patent or the use of which is claimed in a patent[.]” 35 U.S.C. § 271(e)(2)(A). “The patentee bears the burden of proving infringement by a preponderance of the evidence.” SRI Int’l v. Matsushita Elec. Corp., 775 F.2d 1107, 1123 (Fed. Cir. 1985).

“Determining infringement requires two steps. First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or process.” Absolute Software, Inc. v. Stealth Signal, Inc., 659 F.3d 1121, 1129 (Fed. Cir. 2011). “For literal infringement, the patentee must prove that the accused product meets all the limitations of the asserted claims; if even one limitation is not met, there is no literal infringement.” E.I. du Pont De Nemours & Co. v. Unifrax I LLC, 921 F.3d 1060, 1073 (Fed. Cir. 2019).

After considering the evidence presented at trial, I find that Azurity has proven by a preponderance of the evidence that Alkem’s ANDA infringes all asserted claims. I address the two disputed claim limitations below.

1. Presence of pH Adjusters

The asserted claims of the ’621 patent recite an ingredient list preceded by the phrase “consisting essentially of.” By using this phrase, a patentee “signals that the invention necessarily includes the listed ingredients but is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention.” HZNP Medicines LLC v. Actavis Labs. UT, Inc., 940 F.3d 680, 893 (Fed. Cir. 2019) (alterations omitted). Alkem argues that this limitation is not

met because its ANDA contains pH adjusters—sodium hydroxide and hydrochloric acid—that materially affect its pH, which, in turn, impacts stability.

Azurity offers several responses. The first is that the ANDA infringes under the assumption that the pH adjusters will not be added to every batch. In Azurity’s view, the designation “q.s.” for the pH adjusters was a representation to the FDA that Alkem could make a compliant batch without adding the pH adjusters. (See N.T. 142-43, 151 (Little).)

To prove infringement under 35 U.S.C. § 271(e)(2)(A), Azurity must establish that if the ANDA is approved, Alkem “will likely market an infringing product.” Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1570 (Fed. Cir. 1997). Where the ANDA itself “does not clearly describe a product that meets the limitations of the asserted claims,” a court must look to factual evidence bearing on “[w]hat is likely to be sold, or, preferably, what will be sold.” Ferring B.V. v. Watson Labs., Inc., 764 F.3d 1382, 1387-88 (Fed. Cir. 2014) (quotation marks and alterations omitted).

Azurity’s assertion that the pH adjusters will not be added to every batch misreads the ANDA. The designation “q.s.” means that Alkem will add as much sodium hydroxide or hydrochloric acid as needed to achieve the target pH. (N.T. 138, 207.) Whether that amount could be zero is a factual question the ANDA does not answer. (See N.T. 173-74 (Little).) As an analogy, if a recipe were to call for “1 cup of flour and enough water to make the dough hold together,” it would be incorrect to read that as stating that the dough could be made without water or to say that infringement could be proven on the assumption that water would not be added.

Azurity argues that this case is analogous to Sunovion Pharmaceuticals, Inc. v. Teva Pharmaceuticals, Inc., 731 F.3d 1271 (Fed. Cir. 2013). There, Teva’s ANDA permitted it to sell a range of products, some of which would infringe Sunovion’s patent. Id. at 1278. The Federal Circuit held that Teva could not avoid infringement based on “internal manufacturing guidelines”

and a “declaration” that it would limit the products actually sold to ones outside the patent’s scope. Id. Here, unlike in Sunovion, Alkem’s ANDA does not leave Alkem free to add or not add pH adjusters at its discretion. Rather, the ANDA requires pH adjusters to be added whenever the other ingredients do not yield a pH within the specified range. (See PTX-60 at ALK_ENPL_00000402 (“Check the pH of the solution . . . and adjust the pH about 3.30 (ranges 3.00 to 3.60)”); id. at 414 (“If required adjust the pH”).) Thus, Alkem’s ANDA does not authorize Alkem to sell a range of products, some infringing and some not. And, although the ANDA is silent as to how often liquids made using the required procedure will need pH adjustment, “silence does not answer the question of infringement.” See Ferring B.V., 764 F.3d at 1409.⁴

Because the ANDA does not answer the question of whether the pH adjusters will be added to every batch, Azurity “must rely on evidence” to show what product would be sold if the ANDA were approved. See Ferring B.V., 764 F.3d at 1388. Azurity offers only speculation that some batches might vary in pH such that no pH adjustment would be necessary. Contrary to Azurity’s argument, I do not read Alkem’s expert Dr. Rabinow’s statement that sodium hydroxide is “not necessarily” added to every batch as a concession that pH adjustment is sometimes unnecessary. (N.T. 207-09.) Rather, I view this testimony only as an acknowledgment that the ANDA is ambiguous as to how often the pH adjusters will be added. For these reasons, Azurity has failed to prove that Alkem would likely market some batches of its product without pH adjusters.

⁴ At oral argument, Azurity noted that Alkem’s ANDA includes a proposed product label stating that the drug “may” contain sodium hydroxide and hydrochloric acid. But this statement is consistent with the ANDA’s requirement to add pH adjusters whenever the pH is outside of the specified range. And, even if the word “may” in the label carried a negative inference that some units of the product would lack pH adjusters, Azurity cites no authority that Alkem would be allowed to deviate from the product’s specification in the ANDA based on more permissive language in a proposed label.

Azurity next argues that pH adjusters do not matter for infringement because they do not “materially affect the basic and novel properties” of Azurity’s claimed invention. Azurity notes that after the pH of Alkem’s ANDA is adjusted, the final pH will always be within the ranges specified in the asserted claims. Azurity thus reasons that pH adjusters must not materially affect the pH because they do not change whether claim limitations related to the pH are satisfied. But Azurity presented no evidence that Alkem’s ANDA would be stable if its pH were not adjusted. And expert testimony persuasively demonstrated that adding pH adjusters to a liquid does affect its pH, that pH affects stability, and that stability is a basic and novel property of Azurity’s invention. (N.T. 149 (Little); N.T. 200-01 (Rabinow).) Therefore, I agree with Alkem that the pH adjusters, to the extent they are present, “materially affect the basic and novel properties of the invention.”⁵

Importantly, however, I do accept Azurity’s final alternative argument that adding pH adjusters to the mixture does not avoid the “consisting essentially of” limitation. This is because the pH adjusters are consumed and are no longer present once the solution is mixed. On this point, I credit Dr. Little’s testimony that the pH adjuster sodium hydroxide is consumed when it reacts with citric acid. (N.T. 140-43 (Little).) Alkem’s expert Dr. Rabinow essentially conceded that this reaction occurs and that it results in the pH adjusters being eliminated. (N.T. 211-13 (Rabinow).) The products of this reaction are water and sodium citrate, both of which are ingredients listed in the asserted claims (either verbatim or contained within the term “citrate buffer”). (See N.T. 140-43.)

While neither party requested construction of whether the claimed ingredients must be

⁵ I also note that Azurity’s argument that the effect of an unlisted ingredient is not “material” so long as all other claim limitations are met would make the “consisting essentially of” limitation superfluous.

present before or after mixing, claims to a mixture ordinarily go to “a composition that contains the specified ingredients at any time from the moment the ingredients are mixed together.” Mars, Inc. v. H.J. Heinz Co., L.P., 377 F.3d 1369, 1374 (Fed. Cir. 2004) (emphasis deleted). Therefore, the fact that sodium hydroxide is an unlisted ingredient does not preclude infringement provided that the mixture ultimately contains only listed ingredients, and I accept Dr. Little’s explanation that it does. For that reason, Azurity has proven by a preponderance of the evidence that the “consisting essentially of” limitation is met.

2. Buffer Concentration

All asserted claims require that a buffer be present in a certain concentration, such as “wherein the buffer concentration is about 5 mM to about 20 mM.” (’621 patent, Claim 4 (independent claim inserted).) Alkem argues that Azurity has not proven that the ANDA contains a buffer in the same concentration. Specifically, Alkem characterizes Dr. Little’s testimony that the pH adjuster sodium hydroxide reacts with citric acid to form sodium citrate as suggesting that adding pH adjusters alters the buffer concentration, a detail that Azurity’s infringement testimony does not account for. As before, I will analyze the issue under the assumption that pH adjusters will be added to every batch because Azurity has not proven that Alkem would likely market a batch without them.

I credit Dr. Little’s testimony that the buffer concentration in Alkem’s ANDA can be determined by calculating the amounts of citric acid and sodium citrate and adding those two quantities together. (See N.T. 117 (“[Y]ou do this calculation and add them together” to obtain “the total of the buffer concentration”).) I also find convincing Dr. Little’s explanation that when this calculation is performed for Alkem’s ANDA, the result is within the limitation recited in the claim.

Based on these facts, I conclude that the asserted buffer concentration limitations are met.

Alkem asks me to not accept Dr. Little's calculation because he also testified that added sodium hydroxide reacts with citric acid to form water and sodium citrate, which Alkem hypothesizes must "grow" the buffer. But no expert testified that this reaction grows the buffer; rather, Alkem asks me to infer it as a matter of logic. A court must not "dr[aw] on its own knowledge" of technical matters without the aid of expert testimony. See Flash-Control, LLC v. Intel, No. 2020-2141, 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021). And even if Alkem is correct that adding sodium hydroxide could change the buffer concentration, Alkem provided no reason to believe the effect is so substantial that Dr. Little should have accounted for it. For these reasons, Alkem's unsupported hypothesis that adding sodium hydroxide "grows" the buffer does not persuade me to discredit Dr. Little's otherwise convincing calculation that the buffer limitation is met.⁶

Because Azurity has proven by a preponderance of the evidence that Alkem's ANDA meets all asserted claim limitations, I conclude that Alkem's ANDA infringes all asserted claims.

III. OBVIOUSNESS

A. Facts Relevant to Obviousness

1. Background on Liquid Dosage Forms for Drugs

Azurity's claimed invention is a liquid dosage form of enalapril, which is important because not all patients can swallow pills. (See N.T. 104 (Little).) The parties' experts testified to three

⁶ In light of this disposition, it is unnecessary to address Azurity's contention that Alkem forfeited its argument that the addition of pH adjusters affects the buffer concentration. However, I note that the issue in dispute is whether Dr. Little's testimony should be disbelieved because it is internally inconsistent. Given that it was Azurity's burden to present evidence of infringement and "credibility is always at issue," United States v. Green, 617 F.3d 233, 251 (3d Cir. 2010), it is unlikely that Alkem could forfeit its right to point out inconsistencies in Dr. Little's testimony.

ways that liquid dosage forms can be produced. The first is by compounding, in which a pharmacist crushes a tablet and mixes it with a liquid. (N.T. 69 (Beckloff); N.T. 104 (Little).) Compounding has drawbacks in that it creates risks of contamination and causes variation from pharmacy to pharmacy. (N.T. 105 (Little).) A second way is reconstitution, in which the drug is sold as a powder and a pharmacist mixes the powder with a liquid. (N.T. 69 (Beckloff); N.T. 106-07 (Little).) The third way is for the drug itself to be manufactured as a “ready-to-use” (or “RTU”) liquid. (N.T. 107 (Little).) Ready-to-use liquids avoid the contamination issues associated with compounding. (N.T. 107 (Little).)

2. Drug Development Process

The parties agreed that a POSA would have experience developing drug formulations. (N.T. 110-11, 191.) The process by which drug formulations are developed is relevant to understanding whether Azurity’s claimed invention would have been obvious before the priority date.

When developing a drug formulation, a formulator (someone who develops drug formulations) would start with a “target product profile,” which describes the desired characteristics of the drug. (N.T. 258-59 (Constantinides); Mosher⁷ 26.) The target product profile includes the dosage form (such as an oral liquid) and the required stability. (N.T. 259.)

Before the invention at issue, it was known in the art that stability is a critical part of the development of an oral liquid. (N.T. 259 (Constantinides).) For example, a ready-to-use liquid needs to be stable for at least 12 months to account for distribution time. (Mosher 63-64.) The term “stability” encompasses many different kinds of stability: chemical stability, physical stability, stability of taste, stability of smell, and others. (N.T. 328.) This case involves chemical stability.

⁷ Citations to “Mosher” refer to Dr. Mosher’s video deposition transcript.

“The chemical stability of many drugs in solution may be improved by maintaining the pH of the solution in a particular range.” (DTX-1118, de Villiers⁸ at 225; see also Casas⁹ at 272 (“[S]ome active ingredients . . . require a certain pH range to achieve maximum stability in aqueous solution, and in such cases, the pH must be adjusted to the requirements of stability of the preparation.”).) Thus, a formulator developing a drug would determine how the drug’s stability depends on the pH of the formulation. (N.T. 260 (Constantinides).)

Formulators sometimes measure the stability of a drug for a short time and use that data to predict stability over a longer period, a process called “accelerated” stability testing. (N.T. 553 (Little).) Accelerated stability testing can be an “exploratory tool.” (N.T. 553 (Little).) But accelerated stability testing is not always predictive of long-term stability because the way a drug degrades in the short-term can be different than the way it degrades in the long-term. (N.T. 551-52.)

The FDA has published a guidance document, dated November 2003, that “is intended to define what stability data package for a new drug substance or drug product is sufficient for a registration application” (FDA Guidance¹⁰ § 1.1.) For drugs intended to be stored in a refrigerator, the FDA Guidance permits a registration application to use 12 months of stability data at refrigerated temperature or 6 months of stability data at an elevated temperature. (Id. § 2.1.7.2.) The FDA Guidance defines a “significant change” during testing as, among other things, “[a] 5 percent change in assay from [the drug’s] initial value.” (Id. § 2.2.7.1.)

⁸ de Villiers, “Buffers and pH Adjusting Agents” (3d ed., J.E Thomson ed. 2009) (“de Villiers”).

⁹ PTX-78, Casas et al., “Physicochemical stability of captopril and enalapril extemporaneous formulations for pediatric patients,” *Pharm. Dev. & Tech.*, 20(3):271-78 (Nov. 26, 2013) (“Casas”).

¹⁰ DTX-1109, “Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products,” United States Food and Drug Administration (“FDA Guidance”).

3. Buffers

Buffers are used to maintain pH, and their use was basic knowledge for a POSA as of the priority date. (N.T. 192 (Rabinow); N.T. 257 (Constantinides).)

Alkem's expert Dr. Constantinides, Azurity's employee Dr. Mosher, and the published source de Villiers provided consistent information about how a POSA would choose a buffer for a drug, taking into account information such as the desired pH, among other factors (such as the buffer's " pK_a "). (See Mosher 33-35.) de Villiers suggests buffer types appropriate for specific pH ranges, with a citrate buffer being appropriate for a pH of 2.5 to 6.5. (de Villiers at 225-29.) A formulator will also usually have experience with many buffer systems and may rely on experience to choose one. (Mosher 58-59.)

Once the type of buffer is selected, the concentration of the buffer needs to be chosen. The buffer concentration can be determined using well-known chemical principles such as those described in the literature. (N.T. 291-94 (Constantinides, citing de Villiers).) The literature includes example concentrations of citric acid and sodium citrate that can be used to make a buffer suitable over a pH range from 2.5 to 6.5 (de Villiers at 228-30.)

4. Enalapril

Enalapril is a drug used to treat hypertension (high blood pressure). (N.T. 100 (Little).) Before enalapril can affect blood pressure, it must be converted to another chemical called "enalaprilat." (N.T. 100-01 (Little).) But because enalaprilat is not absorbed by the body, the drug that is administered to the patient must be enalapril, which then converts to enalaprilat in the body. (N.T. 103 (Little).)

The reaction that converts enalapril to enalaprilat is called "hydrolysis," and, when enalapril

is mixed with water, it can undergo hydrolysis even when it is not in the human body. (N.T. 100-02 (Little).) It was thus known before the present invention that enalapril can degrade in water, a fact relevant to enalapril's chemical stability. (N.T. 102-03, 454-55 (Little); N.T. 328; Allen¹¹ at 1917-18.)

It was also known in the art that the stability of enalapril in water depends strongly on the pH of the solution. (N.T. 202 (Rabinow); Allen at 1917-18; Al-Omari¹² at 898.) Thus, a formulator seeking to make an oral liquid formulation of enalapril could increase its stability by using an appropriate pH. (Allen at 1918.)

Two prior art sources state that enalapril is most stable when the pH of the solution is near 3. (Allen at 1917; Sosnowska¹³ at 322.) These prior-art teachings are important because a central point in dispute is whether a POSA would have known how to make enalapril stable before Azurity's invention.¹⁴

The parties' experts disagreed how easy it would have been before Azurity's invention to make enalapril stable in water. Alkem's expert Dr. Constantinides testified that it would have

¹¹ DTX-1074, Allen *et al.*, "Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids," *Am. J. Health-Syst. Pharm.*, 55:1915-1920 (Sept. 1998) ("Allen").

¹² DTX-1144, Al-Omari *et al.*, "Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations," *J. Pharm. Biomed. Anal.*, 25(5-6), pp. 893-902 (July 2001) ("Al-Omari").

¹³ DTX-1077, Sosnowska *et al.*, "Stability of extemporaneous enalapril maleate suspensions for pediatric use prepared from commercially available tables," *Acta Poloniae Pharmaceutica-Drug Research*, 66(3):321-26 (2009).

¹⁴ Azurity argued at trial that one or both of these publications may inaccurately cite enalapril's stable pH to another source, *The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals* (12th ed.) (the "Merck Index"). In context, it appears that Allen's citation to the Merck Index corresponds to other information in the same sentence (enalapril's "pK_a values") and does not inaccurately cite the Merck Index for enalapril's stable pH. Sosnowska, on the other hand, does inaccurately cite the Merck Index for enalapril's stable pH.

been “easy” for a POSA to make enalapril in water 95% stable for 24 months at refrigerated temperature through “routine experimentation” based on what was known in the prior art. (N.T. 315-16.) Azurity’s expert Dr. Little opined that a formulator would not consider stability for 18 months an achievable goal. (N.T. 486, 532.) In Dr. Little’s view, “all of the various things in the formulation” are needed to achieve long-term stability, and, therefore, if a POSA attempted to “optimize” an enalapril liquid for stability, any alteration to the formulation could have undesirable effects. (N.T. 500, 526-27.) According to Dr. Little, Azurity managed to make enalapril stable in water by finding a “specific combination of things” that avoids “all of the different reactions that could potentially happen with” enalapril in water. (N.T. 533.)

5. Enalapril Liquid Formulations Predating Azurity’s Invention

The priority date of the asserted patents is March 18, 2016. (Revised (8/14/2022) Uncontested Facts ¶¶ 15, 28.) Prior art publications consist of those that were published and publicly accessible before that date. See VidStream LLC v. Twitter, Inc., 981 F.3d 1060, 1066 (Fed. Cir. 2020).

Liquid dosage forms of enalapril had been developed prior to Azurity’s invention, although no prior liquid form of enalapril met all limitations of any asserted claim. (See N.T. 352 (Constantinides).) In particular, no prior art publication had described an enalapril liquid that was stable for 12 months. (See N.T. 352 (Constantinides).) The liquid dosage forms of enalapril that had been developed before Azurity’s invention are summarized below.

Nahata (June 1998) Nahata describes a study “to determine the stability of enalapril maleate” in various liquids at refrigerated and room temperature.¹⁵ (Nahata¹⁶ at 1156.) Nahata notes that this work was undertaken because there was “limited data on the stability of enalapril in extemporaneously prepared oral liquids” and, in particular, “no known stability data for enalapril in readily available vehicles” (*Id.* at 1155-56.)

Nahata studied enalapril in: (1) water, (2) a citrate buffer solution, and (3) a mixture of the commercially available liquids Ora-Plus and Ora-Sweet. The pHs of these liquids are, respectively, 7.1, 5.1, and 4.7. (Nahata at 1156.) pH is important to the obviousness analysis because enalapril was reported to be more stable at some pHs than others. As noted above, enalapril was known to be most stable at a pH near 3, and Nahata’s Ora-Plus and Ora-Sweet mixture is closest to this value.

Nahata reports data on the stability of the three studied enalapril liquids. Nahata evaluates stability by measuring how much enalapril remains in the liquid over time. The data for the Ora-Plus and Ora-Sweet mixture at refrigerated temperature start at 100.0 plus-or-minus 3.6% at the beginning of the study and end at 95.8 plus-or-minus 5.9% after 90 days, with a visible downward trend in between. (Nahata at 1156.)

Allen (Sept. 1998) Allen reports on a study of liquid forms of various drugs, including enalapril. Like Nahata, Allen studied enalapril in three different liquids: (1) a mixture of Ora-Sweet and Ora-Plus, (2) a mixture of Ora-Sweet SF and Ora-Plus, and (3) cherry syrup. The pHs of these liquids are 4.7-4.8, 4.7-4.8 again, and 3.9. As noted, Allen states that enalapril is most

¹⁵ Refrigerated temperature is 5 plus-or-minus 3 °C. (N.T. 548 (Little).)

¹⁶ DTX-1078, Nahata *et al.*, “Stability of enalapril maleate in three extemporaneously prepared oral liquids,” *Am. J. Health-Sys. Pharm.*, 55:1155-57 (June 1, 1998) (“Nahata”).

stable at a pH near 3, and the pH of the cherry syrup liquid is closest to this value. (Allen¹⁷ at 1918.)

Allen tested the stability of those three enalapril liquids and reports the resulting data. The study runs for a period of 60 days. Some of the tests are done at refrigerated temperature. The reported stability numbers for the cherry syrup liquid at refrigerated temperature start at 97.2 plus-or-minus 1.0% and end at 97.0 plus-or-minus 1.1%. (Allen at 1918.)

Allen also discusses prior work on the stability of enalapril and notes that a prior study found that enalapril liquids with pHs of “2 and 5 were stable for 262 and 114 days, respectively,” at room temperature. (Allen at 1917-18.) Another study mentioned by Allen found that enalapril in a citrate buffer with a pH of 5 was stable for 90 days at refrigerated temperature but not as stable at room temperature. (*Id.* at 1918.) Regarding those prior studies, Allen observes that “[t]hose liquids were buffered to a pH that was 2 units less acidic than the pH at which the drug has maximum stability.” (*Id.* at 1918.) In contrast to those studies, Allen’s enalapril liquids use pHs “somewhat closer to the pH for maximum stability”—i.e., 3. (*Id.* at 1918-19.) Thus, Allen provides evidence that as early as 1998, it was known in the art that a formulator seeking to make an enalapril liquid should use a pH near 3 to achieve the greatest stability.

Al-Omari (2001) Al-Omari’s study provides no information about long-term stable liquids but was offered by Alkem to demonstrate the importance of pH in making enalapril stable. Al-Omari’s primary aim was to study the stability of enalapril in tablets, but Al-Omari’s publica-

¹⁷ DTX-1074, Allen *et al.*, “Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids,” *Am. J. Health-Syst. Pharm.*, 55:1915-1920 (Sept. 1998) (“Allen”).

tion contains information about enalapril liquids as well. (Al-Omari¹⁸ at 893.) Al-Omari studied enalapril liquids with pHs of 10.5, 7.0, 5.5, 3.4, and 2.2. Stability data for each of these liquids are presented in a graph showing how fast each liquid degraded over time. This data was collected at 80 °C for under 140 hours (that is, substantially warmer than refrigerated temperature and substantially shorter than one year). (Al-Omari at 898.)

Al-Omari's graph shows that the enalapril liquid with a pH of 3.4 degraded the slowest among the liquids tested. The liquid with a pH of 2.2 was the next slowest. (Al-Omari at 898; N.T. 196-97 (Rabinow).) Al-Omari concludes from these data that "the rate of enalapril loss is dependent upon the solution pH and it is obvious that the degradation at pH 10.5 is more significant than that at lower pH values." (Al-Omari at 898.) Al-Omari also notes that a prior study had found that the rate at which enalapril degrades "depend[ed] upon [the] pH of the solution[.]" (*Id.* at 894.) Alkem thus offers Al-Omari to support its expert Dr. Rabinow's opinion that pH was known to be the "dominant" driver of the stability of enalapril. (N.T. 195-97, 202 (Rabinow).)¹⁹

Sosnowska (2009) The purpose of Sosnowska's study was to examine enalapril liquids "prepared from commercially available tablets" by compounding. (Sosnowska at 321 (abstract).) According to Sosnowska, "[i]t is important that the drug should be stable in the vehicle for the proposed duration of storage and administration of the product." (*Id.* at 321.)

¹⁸ DTX-1144, Al-Omari *et al.*, "Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations," J. Pharm. Biomed. Anal., 25(5-6), pp. 893-902 (July 2001) ("Al-Omari").

¹⁹ At trial, Azurity pointed out that Al-Omari's graph is poorly labeled and obscures the exact rate at which each studied liquid degraded. (Al-Omari at 898.) Although Alkem's expert Dr. Rabinow relied on Al-Omari for its teaching about the relationship between pH and stability, Dr. Rabinow conceded that Al-Omari's poorly labeled graph was a "mistake." (N.T. 214 (Rabinow).) But Dr. Rabinow pointed out that, even though the exact rate at which each liquid degraded is unclear, he could tell that some of the liquids degraded at least "tenfold . . . , perhaps more." (*See* N.T. 214-15 (Rabinow).)

Sosnowska studied enalapril liquids that all had a pH of 3—the value Sosnowska and Allen give for the pH at which enalapril is most stable. Sosnowska’s liquids used citric acid as a buffer to maintain this pH. (Sosnowska at 322.) Stability data for Sosnowska’s enalapril liquids are reported. Sosnowska tested these liquids for 30 days, some at refrigerated temperature. (Id. at 322.) The average stability after 30 days was at least 98% under all studied conditions. (Id. at 322.)

Casas (Nov. 2013) Casas’s objective was to develop enalapril liquids that could be made by compounding and administered to children. (Casas²⁰ at 271.) To achieve that objective, Casas prepared solutions of enalapril in water and measured the stability of these solutions at various temperatures. The solutions had pHs in the range of 2.55 to 2.78. (Id. at 275.) According to Casas, these liquids are ones that “a Pharmacist could easily prepare with available and low cost materials” (Id. at 272.) Casas also states that paraben preservatives should not be used in these formulations because parabens can cause allergic reactions, especially in infants, newborns, and toddlers. (Id. at 272.)

Casas presents data on the stability of the studied liquids in a graph. At refrigerated temperature, the graph shows no visible change in the amount of enalapril remaining over the 50 days of study. (Casas at 278.) But Casas also states, without corresponding data or points on the graph, that “[a]fter 3 months of study, at the three temperatures studied drug content of [the formulation] decreased by 40%.” (Id. at 277.)

²⁰ PTX-78, Casas et al., “Physicochemical stability of captopril and enalapril extemporaneous formulations for pediatric patients,” *Pharm. Dev. & Tech.*, 20(3):271-78 (Nov. 26, 2013) (“Casas”).

The Epaned Kit and the '747 Patent (Oct. 2013) The next prior liquid formulation of enalapril is Azurity's own "Epaned Kit" product. Prior to inventing a ready-to-use enalapril liquid, Azurity marketed the Epaned Kit, which consisted of an enalapril powder and a liquid (the "diluent") that could be combined to make an enalapril liquid. (N.T. 64-65 (Beckloff).)

Azurity's patent related to the Epaned Kit is U.S. Patent No. 8,568,747 (the '747 patent), which was published on October 29, 2013, and claims enalapril powders that are reconstituted into oral liquids. (See DTX-1094, '747 patent, claim 1.) The '747 patent states that some of the described liquids are "stable" for 36 weeks at "refrigerated and ambient conditions." The patent defines "stable" as "having at least about 90% enalapril and 5% or less total impurities or substances at the end of a given storage period." (*Id.*, col. 13:5-33.) The '747 patent reports stability data for some example reconstituted liquids measured over 12 weeks, including some tests at refrigerated temperatures. The data at refrigerated temperature consistently show at least 95% of the enalapril remaining over the 12 weeks of study. (*Id.*, col. 23.)

Relevant to some of the specific ingredients recited in the asserted claims, the '747 patent includes example liquids in which the concentration of enalapril is 1.0 mg/mL and describes the use of paraben preservatives with an enalapril liquid that is described as "stable." ('747 patent, cols. 5:28-32, 7:51-59, 22:59.) It also describes the use of sweeteners in these enalapril liquids, including sucralose and xylitol. (*Id.*, cols. 7:60-8:37.)

Kit Insert (2014) Azurity's prescribing literature for the Epaned Kit included a document the parties referred to as the "Epaned Kit Insert," which is dated September 2014. (DTX-1073.) The Kit Insert contains information about the composition of the powder and liquid used to make the Kit. It states that the Epaned Kit uses Ora-Sweet SF as the liquid, which contains citric acid

and sodium citrate that are described as a “buffer[.]” (Kit Insert § 11.) It also states that Ora-Sweet SF contains methylparaben and propyl paraben and gives the amounts of these ingredients. (Id.) Dr. Constantinides testified that the amount of preservative stated in the Kit Insert is very close to the concentration of preservative recited in the asserted claims. (N.T. 301-02 (Constantinides).)

The Kit Insert further states that the Kit powder contains mannitol, a fact Azurity offered in an effort to show that an enalapril liquid made without mannitol (as some asserted claims require) would not have been obvious. Mannitol is a “bulking agent” used in powders. (N.T. 265, 306 (Constantinides).) According to Alkem’s expert Dr. Constantinides, a POSA attempting to make a long-term stable solution of enalapril in water would not try adding mannitol because it is not needed. (N.T. 265.) Azurity’s expert Dr. Little disagreed and stated that mannitol has uses in liquid formulations, including as a sweetener and as a “tonicity agent.” (N.T. 492-93.) Dr. Little also testified that mannitol can be used as a “stabilizing agent.” (N.T. 492.)

6. Issues with Prescribing Enalapril to Children Before the Present Invention

Azurity presented evidence that before the Epaned Kit became available, physicians prescribing enalapril to children would use compounding, a practice with numerous drawbacks. Azurity also attempted to show that there were drawbacks to using its own Epaned Kit product, although for the reasons explained below, that testimony was largely speculative.

As of 2014, enalapril was the only anti-hypertensive drug that was usable by a broad age range of patients. (N.T. 403-04 (Mahan).) Given the lack of alternatives, Azurity’s expert Dr. Mahan prescribed enalapril to children before there was a liquid form available, coming up with work-arounds when patients could not swallow pills. (N.T. 404-05.) As described above, some of these work-arounds, such as compounding, created safety risks.

Azurity's Epaned Kit was an improvement over compounding, leading Dr. Mahan to use the Kit over compounding. (N.T. 422-23.) The Kit became available in 2013 and was safe and effective. (N.T. 439 (Mahan).) Even with the Kit, Dr. Mahan was still concerned that pharmacies might make mistakes because many steps were involved in reconstitution. Dr. Mahan sometimes suspected that pharmacies made errors with reconstitution. (N.T. 423-25.) Azurity's head of research and development Mr. Beckloff also testified that he believed pharmacy technicians sometimes made errors with the Kit, including using the wrong diluent, poking a pen through the seal, and causing contamination with fibers from the pharmacist's sweater. (N.T. 65-66.)

But Dr. Mahan could not identify a specific instance in which a pharmacy reconstituted the Kit incorrectly. He had only heard "stories." (N.T. 440-43.) Mr. Beckloff testified that an error that resulted in a liquid of the wrong concentration would have "safety implications," but did not testify that any such error occurred. (N.T. 66.)

B. Discussion—Obviousness

"A patent for a claimed invention may not be obtained ... if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. The accused infringer bears the burden of proving invalidity by clear and convincing evidence. Microsoft Corp. v. i4i Ltd. Partnership, 564 U.S. 91, 95 (2011). The obviousness inquiry is "flexible" and "functional." KSR Int'l Co. v. Teleflex Inc. 550 U.S. 398, 415 (2007). "[A] court can take account of the inferences and creative steps that a [POSA] would employ." Id. at 418. But analysis based on hindsight is forbidden. Insite Vision Inc. v. Sandoz, Inc., 783 F.3d 853, 859 (Fed. Cir. 2015). An

invention is not obvious merely because it is “sufficiently simple to appear obvious to judges after the discovery is finally made.” Outside the Box Innovations, LLC v. Travel Caddy, Inc., 695 F.3d 1285, 1298 (Fed. Cir. 2012).

“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” KSR, 550 U.S. at 418. Rather, it must be shown “by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.” In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1068-69 (Fed. Cir. 2012). “In considering motivation . . . , the problem examined is not the specific problem solved by the invention,” because “[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.” Insite Vision Inc. v. Sandoz, Inc., 783 F.3d 853, 859 (Fed. Cir. 2015). Rather, motivation must be viewed from the perspective of the prior art. Id.

“The ultimate judgment of obviousness is a legal determination.” KSR, 550 U.S. at 427. The court must make subsidiary factual findings as to: “(1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness.” In re Cyclobenzaprine Hydrochloride, 676 F.3d at 1068; see also Graham v. John Deere Co., 383 U.S. 1, 17 (1966); KSR, 550 U.S. at 415.

The parties agree that all ingredients in the asserted claims, including enalapril itself, were individually known prior to Azurity’s invention, and that it was known that enalapril could be mixed with water to make a liquid dosage form. Azurity also did not seriously challenge Alkem’s evidence that it was known that enalapril liquids could include buffers, preservatives, sweeteners,

and flavors—including the same choices for these ingredients as used in the asserted claims. Notably, at the time of the invention at issue, Azurity itself marketed the Epaned Kit, which contained enalapril in the claimed concentration, a citrate buffer, sweeteners, and paraben preservatives. (Kit Label § 11.)

It was, however, also undisputed that the prior art did not disclose any liquid formulation of enalapril known to be stable for a year or more at refrigerated temperature. The parties disagree as to whether a POSA would have expected, before Azurity's invention, that enalapril in water could be as stable as the asserted claims require. The parties also disagree as to whether it would have been obvious to use the particular combination of ingredients recited in the claims.

For the reasons discussed below, I find that Alkem has proven by clear and convincing evidence that the asserted claims would have been obvious to a POSA as of March 18, 2016. Alkem's evidence persuasively established that a POSA would have expected that enalapril could be stable for a year or more in water at refrigerated temperature. I also credit Alkem's interpretation of the prior art that enalapril in water would be most stable if combined with a buffer to keep the pH at "about 3," a range that includes claimed pHs near 3.3. The remaining ingredients—flavors, sweeteners, and preservatives—were known, and the requirements of a manufactured oral liquid would provide a motivation to combine these known ingredients into a single product. The result is Azurity's claimed invention.

1. Expectation of Success in Developing a Long-Term Stable Enalapril Liquid

The heart of the parties' obviousness dispute is whether a POSA would have reasonably expected that enalapril in water could be as stable as the claims require—that is, at least 95% stable at refrigerated temperature after 12, 18, or 24 months. To prove that Azurity's invention

was obvious, Alkem must establish that “a [POSA] would have had a reasonable expectation that” attempting to make a long-term stable enalapril liquid “would succeed.” Leo Pharmaceutical Prods. v. REA, 726 F.3d 1346, 1357 (Fed. Cir. 2013). For Alkem to meet this burden, “the expectation of success need only be reasonable, not absolute.” Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007). It is not enough for Alkem to show that it would have been “obvious to try” making a long-term stable enalapril liquid, but, at the same time, “absolute predictability of success is not required.” Id. at 1365. And the fact that any candidate stable enalapril liquid would require “verifi[cation] through testing” does not necessarily mean that a POSA would not reasonably expect the attempt to succeed. Id. at 1364.

No prior art reference states either that it was or was not possible to make an enalapril liquid that was 95% stable for 12 to 24 months at refrigerated temperature. The longest examples of stability mentioned in the prior art are in: (1) the ’747 patent, which states that some liquids are 90% stable for 36 weeks (252 days) at an unspecified temperature; and (2) a prior study mentioned in Allen, which reportedly produced enalapril liquids stable for 262 days (at an unspecified percentage) at room temperature despite using a non-optimal pH. (See ’747 patent, col. 13:5-33; Allen at 1917-18.) On the other hand, no prior art reference includes data showing that enalapril in water at refrigerated temperature and a pH near 3 was less than 95% stable for the duration of whatever test was conducted. Thus, prior art publications did not conclusively reveal whether enalapril in water at a pH near 3 could be stable for 12 to 24 months.

Azurity interprets this state of the art as teaching that enalapril was generally unstable in water and that long-term stability was out of reach. Azurity’s expert Dr. Little testified that the “breadcrumbs” in the prior art suggesting how to achieve long-term stability were too thin to create a likelihood of success. (N.T. 487-89.) Dr. Little also considered it significant that prior art studies

of enalapril used various pHs, some quite different than Allen's reported most stable pH of 3. (N.T. 488.)

Alkem responds that a POSA would have expected that enalapril could be stable in water. Alkem's counsel acknowledged that the prior art did not provide a "direct road map" for making enalapril stable, but Alkem's expert Dr. Constantinides testified that it would be an "easy task" to make an enalapril liquid stable for 18 or 24 months based on knowledge in the prior art. (N.T. 320 (counsel); N.T. 316, 371 (Constantinides).) Specifically, Dr. Constantinides testified that a POSA would be motivated to optimize the stability of an enalapril liquid to 12, 18, preferably 24 months and would have known how to do so, making such level of stability expected. (N.T. 308, 321-22, 355 (Constantinides).)

The parties agree on the contents of the prior art but disagree as to how a POSA would interpret statements in those publications. First, the parties disagree how a POSA would interpret positive statements expressing that enalapril could be stable in water. For example, Allen shows high stability at a pH of 3.9 over 60 days at refrigerated temperature and concludes that these liquids "were stable" for the duration of the test; Sosnowska shows enalapril liquids with a pH of 3 that are at least 98% stable over 30 days at refrigerated temperature; Nahata shows an enalapril liquid with a pH of 4.7 having 95.8% of the enalapril remaining after 91 days and concludes that "enalapril maleate is stable in widely available vehicles"; Casas shows a graph with no visible change in enalapril concentration at pHs of 2.55 to 2.78 over 50 days refrigerated temperature (although Casas mentions, without data, significant degradation after 90 days); and the specification of the '747 patent states that liquid formulations exist that are 90% stable for 36 weeks (which is 252 days or 69% of a year).

Dr. Constantinides opined that these studies would have given a POSA confidence that

long-term stability was possible. (See N.T. 382-84.) I find his opinion convincing. The stability of enalapril had been investigated numerous times and was always found to be sufficiently stable for the application at hand. And, with the exception of one sentence unaccompanied by data in Casas, no study had shown any substantial degradation of enalapril in water at a pH near 3 and refrigerated temperature. Contrary to Azurity's interpretation, the prior art simply does not convey an impression that enalapril is generally unstable in water.²¹

Azurity advocates that an expectation of success has not been proven on several grounds. First, Azurity notes that Dr. Little testified that extrapolating from prior-art data to the high level of stability required by the claims (95% at 12, 18, or 24 months) was too speculative to give a POSA hope that the high level of stability required by the claims could be achieved. But Dr. Little's opinion placed too much emphasis on studies of enalapril under conditions that were known not to be ideal. Such studies show only that some prior researchers who were not trying to achieve long-term stability made formulations that were not long-term stable, not that long-term stability was difficult to achieve.

For example, prior-art publications that studied the feasibility of compounding used commercially available liquids to evaluate whether an enalapril mixture made from those liquids could

²¹ Alkem also asks me to consider the fact that formulators commonly use accelerated stability testing, in which degradation is measured at elevated temperatures. I agree with Alkem that this fact is relevant, but will give it less weight because no expert clarified how far the stability data in the prior art could be extrapolated. Alkem attempted to elicit this testimony from Dr. Constantinides, but it was objected to on the ground that it went outside the scope of his report, and the question was withdrawn. (N.T. 271-76.) I also place little weight on Alkem's reference to the stability of enalapril powders described in the '747 patent because I credit Dr. Little's testimony that enalapril was known to react with water and a POSA would not view the stability of enalapril powder as indicative of its stability in water. Nevertheless, for the reasons stated above, I am ultimately persuaded by Dr. Constantinides's view that the prior art would have conferred an expectation of success that enalapril could be long-term stable in water.

be left on the shelf, unrefrigerated, for short periods of time. (E.g., Casas at 272 (developing an enalapril liquid that “a Pharmacist could easily prepare with available and low cost materials”); Allen at 1918 (using Ora-Sweet and cherry syrup); Sosnowska at 321 (using “commercially available tablets”); Nahata at 1155-56 (using “readily available vehicles”); N.T. 558 (Little) (prior art studies were not trying to achieve long-term stability); N.T. 373-74 (Constantinides) (Nahata was using “commercially available vehicles”).) Allen itself makes the point that prior studies that used a pH of 5 rather than 3 may not be indicative of the stability that could be achieved at a pH closer to 3. (Allen at 1918.) I find that a POSA would not be dissuaded by these studies from believing that long-term stability was achievable.

Azurity also points to a sentence in Casas stating that “[a]fter 3 months of study, at the three temperatures studied drug content of [the formulation] decreased by 40%.” (Casas at 277.) Azurity notes that although Casas was studying compounded liquids, it included liquids with pHs of 2.78 (which Dr. Constantinides testified was “about 3”) that were stored at refrigerated temperatures. I agree with Azurity that Casas could suggest to a POSA that it was possible to make an enalapril liquid that was not stable in water at refrigerated temperature for more than 90 days even if a pH near 3 were used. Dr. Constantinides also acknowledged that the stability data presented in Casas is not predictive of 12 months of stability. (N.T. 347-48.) However, in the context of the other prior art, I conclude that Casas would not dissuade a POSA or teach away from expecting success in making a long-term stable enalapril liquid. Notably, the ’747 patent mentions that some liquids created by mixing enalapril in Ora-Sweet SF remain at least 90% stable after 252 days. (’747 patent, cols. 13:5-33.) Thus, a POSA could interpret Casas’s mention of 40% degradation after 90 days not as the inevitable result of putting enalapril in water but as only the result of “[that] particular study.” (See N.T. 347 (Constantinides).) And, moreover, Casas was not attempting to

achieve long-term stability, Casas's graph contains no data beyond 60 days, and Casas discarded test formulations after 30 days due to microbial contamination. (Casas at 275.)

I also find that Dr. Little's testimony overemphasized the way prior art references defined "stable" rather than the level of stability that was actually achieved. For example, Dr. Little opined that a POSA would not expect that 95% stability was achievable because Sosnowska defined "stable" as at least 90% enalapril remaining, even though the data in Sosnowska showed that the average amount of enalapril remaining at the end of the test period was at least 98%. (N.T. 517-18; Sosnowska at 322.) Similarly, the fact that prior-art researchers collected data for less than a year reflects the requirements of compounding and does not convey the researchers' view that the drug would become unstable after the testing period. (E.g., Nahata at 1157 (concluding that enalapril "is stable" based on short-term studies).)

Throughout trial, Azurity pointed to the 60-day shelf life of its Epaned Kit as evidence that the two-year stability of the present invention was a dramatic improvement. (E.g., N.T. 64-65, 74 (Beckloff).) But the present invention claims stability at refrigerated temperature, not room temperature. No witness testified how long the Kit liquid would be stable if it were kept refrigerated. And Azurity's ready-to-use Epaned product also has a shelf-life of 60 days when not refrigerated, the same as the Kit. (N.T. 74 (Beckloff).) The comparison Azurity attempts to draw between the present invention and the Epaned Kit is therefore uninformative.

Azurity also directs me to FDA guidance stating that a "registration application" submitted to that Agency should contain stability data spanning at least 6, and preferably 12 months. (FDA Guidance §§ 1.1 (scope), 2.2.7.) I do not find the FDA's guidance informative on the question before me. The rigor of testing needed to approve a product is naturally greater than that needed to confer an expectation of success, which "need only be reasonable, not absolute." Pfizer v. Apotex,

480 F.3d at 1364.

For these reasons, I find that Alkem has proven by clear and convincing evidence that the prior art would have led a POSA to expect success in making a long-term stable enalapril liquid. The prior art did not show that enalapril's long-term stability in water was guaranteed, or that it would necessarily be stable for any particular length of time or meet any particular threshold. But the prior art did confer a reasonable expectation that mixing enalapril with water and adjusting the pH to about 3 could result in a drug that was highly stable for a long period of time.

2. Motivation to Make an Enalapril Liquid Long-Term Stable

Alkem must also prove that a POSA would be motivated to make an enalapril liquid as stable as the claims require. Motivation “may be found in many different places and forms.” PAR Pharmaceutical, Inc. v. TWI Pharmaceuticals, Inc., 773 F.3d 1186, 1197 (Fed. Cir. 2014). It “does not have to be explicitly stated in the prior art, and can be supported by testimony of an expert witness regarding knowledge of a person of skill in the art at the time of invention.” Id.

I conclude that a POSA would know that it was necessary to make an enalapril liquid with long-term stability due to the requirements of distribution time and the FDA's requirements regarding shelf-life. (See, e.g., N.T. 63-64 (Beckloff); N.T. 316 (Constantinides); Sosnowska at 321 (“It is important that the drug should be stable in the vehicle for the proposed duration of storage and administration of the product.”).) Dr. Constantinides also credibly testified that a formulator making a ready-to-use liquid would want it to be as stable as the product already on the market—the Kit—which was 24 months. (N.T. 379.) The FDA's guidance provides a motivation to measure stability with a 95% threshold because it defines a “significant change” as, among other things, “[a] 5 percent change in assay from [the drug's] initial value.” (FDA Guidance § 2.2.7.1.) Thus, a

POSA would have been motivated to make an enalapril formulation as stable as the claims require.

Azurity posits that once the Epaned Kit became available, there was no longer a motivation to make enalapril stable enough to be used as a ready-to-use liquid. But Alkem does not need to show that a ready-to-use liquid was a better way to make a liquid dosage form of enalapril than the Epaned Kit, just that it was a “suitable” way “from which the prior art did not teach away.” PAR Pharmaceutical, 773 F.3d at 1197-98. I find that Alkem has met that burden.

3. Achieving Claimed Stability

Alkem must also show that it would have been obvious to a POSA “how” to make an enalapril liquid as stable as the claims require. See In re O’Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988) (invention not obvious where prior art did not teach “how to achieve it”).

I disagree with Alkem that the stability limitations would have been obvious through the doctrine of “inherency,” which renders a claim limitation obvious if it is “the natural result of the combination of elements explicitly disclosed by the prior art.” PAR Pharmaceutical, 773 F.3d at 1196. No evidence was offered at trial that the claimed stability was a “property[] inherently possessed” by any formulation made prior to Azurity’s invention. Persion Pharmaceuticals LLC v. Alvogen Malta Operations Ltd., 945 F.3d 1184, 1190 (Fed. Cir. 2019). Alkem also failed to establish that stability is “necessarily present” in the combination of claimed ingredients. See In re Kubin, 561 F.3d 1351, 1357 (Fed. Cir. 2009).

But I agree with Alkem that the claimed stability would have been obvious because a POSA would have known how to achieve it through “routine application of a well-known problem-solving strategy.” Pfizer v. Apotex, 480 F.3d at 1368 (quotation marks omitted); see also Jerry Harvey 809 F. App’x 919, 922-23 (Fed. Cir. 2020) (finding obviousness where there was a motivation

to achieve the claimed result, an expectation of success in doing so, and capability to achieve it through routine experimentation). A formulator would have been immediately guided to focus on adjusting a single variable, the pH. The prior-art literature strongly conveys that pH drives the stability of enalapril in water and does not suggest that any other variable should be adjusted. (Azurity's contention with respect to mannitol is discussed later.) In view of these teachings, I accept Dr. Constantinides's opinion that this optimization would have been "easy" through "routine experimentation." (N.T. 316, 352; see also N.T. 469 (Little) (noting the ease with which a formulator could make formulations and test them for stability).) The variable was known, the target range (about 3) was known, and the method of adjusting and testing was known. For example, Al-Omari provides a clear template for a POSA to prepare enalapril formulations at a range of pHs within the target range and test the stability of each formulation.

In addition, a formulator would not have needed to wait years for the experimental formulations to degrade; the formulator would have stored the preparations at an elevated temperature and measured the rate of degradation, as in Al-Omari. Azurity criticizes the use of accelerated stability studies, but those criticisms are unavailing. Azurity's first criticism is that accelerated stability results can be misleading because different reactions can occur in the short and long term, such that a solution that appears stable short-term can "fall off a cliff" when tested for longer. But the vague suggestion that short-term stability tests can, in theory, be misleading does not inform whether they would have been misleading for enalapril specifically. Dr. Little did not testify that enalapril degrades differently in the short and long term. Azurity's second criticism is that short-term stability cannot guarantee long-term stability. For example, the FDA does not accept short-term stability tests for use in demonstrating that a formulation is stable for 12 months. But a POSA would not have to conclude that long-term stability was guaranteed to choose a formulation

for long-term testing.

Although Azurity makes a principled argument that optimizing pharmaceutical formulations can sometimes be a daunting task due to the number of variables potentially involved, the facts of this case show that optimizing the stability of enalapril in water is a narrower task that does not involve many variables. “[O]bviousness law . . . recognizes an important distinction between combining known options into a finite number of identified, predictable solutions and merely throwing metaphorical darts at a board in hopes of arriving at a successful result[.]” Leo Pharmaceutical Prods., 726 F.3d at 1357 (citations and quotation marks omitted); see also Adapt Pharma Operations Ltd. v. Teva Pharmaceuticals USA, Inc., 25 F.4th 1354, 1383 (Fed. Cir. 2022) (a “‘general motivation’ to experiment” does not make an invention obvious). Thus, “the discovery of an optimum value of a variable in a known process is usually obvious,” in contrast to situations “where there are ‘numerous parameters’ to try.” Pfizer v. Apotex, 480 F.3d at 1368. In addition, a narrow range within which to optimize (a pH of about 3) was known. See In re Cohen, 767 F. App’x 985, 988-89 (Fed. Cir. 2019) (finding optimization within a range known in the prior art to be obvious); In re Peterson 315 F.3d 1325, 1329-30 (Fed. Cir. 2003) (selecting within a range known in the prior art usually obvious). Optimizing a known variable within a known range is a more straightforward task than the open-ended problem of finding some combination of ingredients that achieves stability.

Given all of the above, I find that Alkem has proven by clear and convincing evidence that a POSA would have been able to make a liquid formulation that was long-term stable at refrigerated temperature through routine application of the known method of adjusting the formulation and testing for stability.

4. Choosing the Claimed pH

Some of the asserted claims require that the formulation have a pH within a certain range. The narrowest of these limitations requires that the pH be “about 3.3.” (E.g., ’621 patent, Claim 7.) Alkem therefore must prove that the asserted claims remain obvious when these limitations are included.

A POSA seeking to develop a liquid formulation of enalapril would review published literature and conclude that the pH at which enalapril was most stable in water was about 3. (Mosher 30 (discussing literature review in general); N.T. 202 (Rabinow); N.T. 260 (Constantinides); Allen at 1917-18; Al-Omari at 898; Casas at 272.) Dr. Constantinides’s opinion that a POSA would view 3.3 as “about 3” is credible in light of Allen’s statement setting the cut-off for stability at about 2 units away from optimal. (See Allen at 1917 (“At a pH >5, the rate of decomposition increases.”); id. at 1918 (“Those liquids were buffered to a pH that was 2 units less acidic than the pH at which the drug has maximum stability.”).)

Azurity criticizes the reported optimal pH based on the fact that two references reporting it—Allen and Sosnowska—include a citation to the Merck Index, which lacks that information. In context, however, it appears that Allen cites the Merck Index only for the “pK_a value” of enalapril. (See Allen at 1917; Sosnowska at 322; Merck Index at No. 3605.) I conclude that a POSA would not infer from the Merck Index citations that Allen was incorrect about the maximally stable pH.

Azurity also counters that some published studies on enalapril liquids used pHs other than 3. (E.g., Allen at 1918; Nahata at 1156.) However, those sources do not represent the formulations they describe to be ideal, and several studies expressly state that they used readily available liquids rather than liquids optimized for stability. (E.g., Casas at 272 (developing an enalapril liquid that “a Pharmacist could easily prepare with available and low cost materials”); Allen at 1918 (using

Ora-Sweet and cherry syrup); Sosnowska at 321 (using “commercially available tablets”); Nahata at 1155-56 (using “readily available vehicles”); N.T. 559 (Little) (“the prior art do not state that in those publications the goal was to achieve” long-term stability); N.T. 373 (Constantinides) (Nahata was an “academic investigation”).) A POSA would not read these publications as suggesting that a pH other than those near 3 should be used.

Alkem does not contend that a formulator in 2016 would have known before trying to choose 3.3 from among the pHs that are about 3, but takes the position that a formulator would have “optimized” the formulation to find the right pH—that is, tried different values until stability was achieved. For the reasons stated previously, a POSA would have expected success in optimizing stability through pH adjustment and would have been able to achieve the claimed stability through “ordinary skill and common sense” rather than “innovation.” KSR, 550 U.S. at 402-03. In particular, a POSA would have focused on pH as the variable to adjust and would have known to adjust it within the range of pHs that are about 3, including 3.3. “[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.” In re Boesch, 617 F.2d 272, 276 (Fed. Cir. 1980).

For these reasons, I find that Alkem has proven by clear and convincing evidence that the pH limitations of the asserted claims would have been obvious in combination with the other limitations.

5. Choosing the Claimed Ingredients

Alkem must also show, by clear and convincing evidence, that the particular formulation Azurity claimed would have been obvious, including the particular combination of all claimed ingredients. This inquiry “requires assessment of the invention as a whole.” Princeton Biochem-

icals, Inc. v. Beckman Coulter, Inc., 411 F.3d 1332, 1337 (Fed. Cir. 2005). “This ‘as a whole’ assessment of the invention requires a showing that an artisan of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would have selected the various elements from the prior art and combined them in the claimed manner.” Id. “[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” KSR, 550 U.S. at 418.

In evaluating whether a POSA would have been motivated to combine ingredients known in the prior art, I find that the process of drug formulation is instructive. The testimony of Dr. Constantinides, which was consistent with that of Dr. Mosher, was that a formulator begins with the product’s desired characteristics—its “target product profile”—and proceeds by selecting ingredients to meet that goal. Thus, the process of formulation provides a motivation to combine elements needed to meet the target properties of the drug, such as combining a preservative (needed for a drug stored in a multi-use container) with a sweetener (needed for a drug administered orally to children). This process also provides a motivation to combine these ingredients with the stability and pH limitations, as a liquid containing these ingredients would need to be stable for the reasons stated above and would need to have a pH at which enalapril is stable.

With that background in mind, I note that it was generally known in the prior art that enalapril could be mixed with water, that those liquids should use pH at which enalapril is stable, that a buffer could be used to maintain the pH, and that enalapril liquids should include sweeteners and preservatives necessary for liquids that are stored in a bottle and orally administered to children. (See N.T. 259, 288-89, 303 (Constantinides); Mosher 70.) In addition, the particular choices of buffers, sweeteners, and preserves claimed were individually known and—more impor-

tantly—known to be usable with enalapril. (See, e.g., Kit Label § 11; '747 patent, col. 8.) Several of them are found in Azurity's own Epaned Kit.

Thus, a formulator seeking to make a ready-to-use enalapril liquid would know to mix enalapril with water, include a buffer to keep it at a pH near 3, and add the other ingredients required by the target profile of an oral liquid stored in a bottle, including a sweetener like sucralose and a preservative such as a mixture of parabens. That is, essentially, the entirety of Azurity's invention. While Azurity claims it found a "specific combination of things" that avoids "all of the different reactions that could potentially happen with" enalapril in water, the steps Azurity took to achieve that goal were largely to try the obvious combination of ingredients and realize that they worked.

Azurity disagrees with this characterization of its invention for several reasons. First, Azurity stresses that it would not have been obvious to take a given enalapril liquid described in the prior art and change its characteristics to match the claimed invention—for example, taking the Epaned Kit and removing mannitol. But the testimony at trial was that drug formulators do not work by taking existing formulations and adding or deleting ingredients. Rather, a formulator would work from a target product profile and add those ingredients required to meet it. (See N.T. 258-59 (Constantinides); Mosher 26.) Dr. Mosher specifically testified that a POSA seeking to make an enalapril liquid would not start with the commercially available liquid Ora-Sweet and attempt to reverse engineer it because determining the effect of each of its numerous ingredients would be prohibitively complicated. (Mosher 69.) Thus, the fact that a prior art reference used, for example, a different preservative than the claimed one does not make the claimed preservative nonobvious if it would have been obvious to a POSA to use the claimed preservative to meet the target product profile.

Azurity next argues that its specific choices of claimed ingredients were not obvious, either

individually or in combination. I address those specific ingredients below.

Choice and Concentration of Buffer The choice and concentration of the claimed buffer follow from the known stable pH of enalapril. Relying on de Villiers, a formulator would have selected a buffer made from sodium citrate and citric acid because de Villiers reports that such a buffer can be used at a pH near 3. And de Villiers shows that determining an appropriate buffer concentration for the target pH would have been routine. The need to make the drug stable would have provided a motivation to combine such a buffer with the other claim limitations.

Preservative and sweetener The need to use a preservative and sweetener follow from the drug's target product profile as an oral liquid, which also provides the motivation to combine these ingredients with the other claim limitations. Azurity's choice of preservative (parabens) and sweetener (sucralose) were known and known to work with enalapril. ('747 patent, cols. 5:28-32, 7:51-59, 7:60-8:37, 22:59; Kit Insert § 11; N.T. 301-02 (Constantinides).) To the extent other preservatives and sweeteners were also known to work with enalapril, a claimed design choice need not "be the best option" to be obvious; it only needs to be "a suitable option from which the prior art did not teach away." PAR Pharmaceutical, 773 F.3d at 1197-98.

Azurity argues that Casas would dissuade a formulator from using preservatives—and, in particular, paraben preservatives—because it states that some patients (especially children) are allergic to them. But Casas made that statement in the context of compounded liquids with short shelf lives, and indeed some of Casas's liquids showed "microbial contamination" after just 30 days. (Cases at 275.) By contrast, a drug in a multi-use container needs a preservative. (Mosher 70.) Casas therefore does not teach that preservatives should not be used in a liquid intended for long-term storage. I also note that Azurity does not claim that its invention dealt with the allergy

risks of parabens any differently than the prior art; rather, Azurity used a known ingredient with all its known advantages and disadvantages.

I therefore conclude that Alkem has proven that Azurity's choice of preservative and sweetener, and its decision to include a flavoring agent, would have been obvious in combination with the other claim limitations.

Absence of Mannitol and Silicon Dioxide Claim 18 of the '482 patent requires that the invention not contain mannitol. In addition, all claims of the '621 patent require that the invention not contain unlisted ingredients that "materially affect the basic and novel properties of the invention," which potentially excludes mannitol and silicon dioxide. Azurity argues that a POSA would not think it obvious to make a formulation without mannitol because the '747 patent describes mannitol as a "stabilizing agent." (See N.T. 492-93 (Little).) The '747 patent also includes stability data for three liquids reconstituted from powders—one powder made with mannitol, one made with lactose, and the other made with sucrose—and states that the powder made with mannitol was most stable. ('747 patent, col. 23.)

I find that Azurity's argument is inconsistent with how a POSA would choose ingredients for a ready-to-use enalapril liquid. A formulator would not start with the formulation described in the '747 patent and attempt to modify it to achieve long-term stability. (Mosher 69.) Rather, a formulator would start with a target product profile and add those ingredients required to meet it. I credit Dr. Constantinides's testimony that a formulator working in this way would simply not introduce mannitol because it is rarely used in liquids.

Because I find that a POSA would have no reason to include mannitol in a ready-to-use enalapril liquid, its absence would have been obvious. To the extent the claims of the '621 patent

also exclude silicon dioxide, the same reasoning applies.

6. Secondary Considerations

In determining whether patent claims are obvious, secondary considerations of nonobviousness must be considered. Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1557 (Fed. Cir. 1985). Azurity offers three: (1) unexpected results, (2) failure of others, and (3) long-felt but unresolved need.

Alkem makes a threshold argument that no secondary considerations apply because any such considerations would lack a nexus to the claimed invention. “In order to accord substantial weight to secondary considerations in an obviousness analysis, the evidence of secondary considerations must have a ‘nexus’ to the claims, i.e., there must be a legally and factually sufficient connection between the evidence and the patented invention.” Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1373 (Fed. Cir. 2017) (quotation marks omitted). “The patentee bears the burden of showing that a nexus exists.” Id. Alkem argues there is no nexus in this case because Azurity happens to market a commercial enalapril product—Epaned RTU—that does not practice the asserted claims.

I disagree with Alkem’s nexus argument. The nexus rule is that the evidence of secondary considerations must relate to the “the patented invention,” not necessarily to any particular product. See Fox Factory, 944 F.3d at 1373. Azurity must show a nexus, but it is a nexus between the evidence and the claims, not between the claims and an unrelated commercial product.

With that understanding, I consider Azurity’s evidence of secondary considerations.

Unexpected Results “To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art,

and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention.” Bristol-Meyers Squibb Co. v. Teva Pharmaceuticals USA, Inc., 752 F.3d 967, 977 (Fed. Cir. 2014). “While a ‘marked superiority’ in an expected property may be enough in some circumstances to render a compound patentable, a ‘mere difference in degree’ is insufficient.” Id.

The parties’ experts disagreed as to whether it would have been unexpected as of March 2016 that an enalapril formulation using the claimed ingredients would have been stable, with Dr. Little testifying that the stability was unexpected and Dr. Constantinides testifying that it was not. (N.T. 321-22 (Constantinides); N.T. 534 (Little).) For the reasons discussed previously with respect to expectation of success, it was not unexpected that enalapril would be stable in water at refrigerated temperature for 24 months. (See, e.g., N.T. 321-22 (Constantinides).) Although the exact stability was not known, published studies suggested it was likely enalapril could be stable long-term. This secondary consideration does not apply.²²

Failure of Others Evidence that others “tried but failed” to make the claimed invention “is particularly probative of obviousness.” In re Cyclobenzaprine Hydrochloride, 676 F.3d at 1082. Azurity did not offer evidence that anyone tried and failed to make a liquid form of enalapril that was long-term stable. Some prior art references described enalapril liquids that were not long-term stable, but, for the reasons discussed previously, none of these authors were trying to achieve long-term stability. This secondary consideration therefore does not apply.

²² Alkem asks me to disregard Azurity’s contention of unexpected results because the evidence Azurity used to support this contention before the Patent and Trademark Office (PTO) consisted of formulations that lacked parabens and therefore did not practice the asserted claims. Given my finding that Azurity’s invention was not unexpectedly stable, it is unnecessary to reach Alkem’s alternative argument. However, I note that while Azurity does have to prove that any unexpected results have a nexus to the asserted claims, Alkem has not pointed to any prohibition on using evidence gleaned from alternative formulations to support that conclusion.

Long-Felt but Unresolved Need “Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious.” Apple Inc. v. Samsung Electronics Co., 839 F.3d 1034, 1056 (Fed. Cir. 2016).

Whether there was a long-felt but unresolved need is typically assessed as of the filing date. Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc., 566 F.3d 989, 998 (Fed. Cir. 2009). By the filing date here (March 2016), the Epaned Kit was available, and Azurity has not shown that there was a long-felt but unresolved need for an enalapril liquid that was ready-to-use as opposed to a powder kit. The problems Dr. Mahan attempted to identify with the Epaned Kit were speculative, as he could not name a single instance of a pharmacy reconstituting the Kit incorrectly. (N.T. 440-43.) Similarly, Dr. Mahan’s comparison of shelf-life between the Epaned Kit and Epaned RTU is uninformative because it compared the Kit’s unrefrigerated shelf-life after compounding to the RTU’s refrigerated shelf-life from the date of manufacture. (See N.T. 434-36.) For these reasons, I conclude there did not exist a long-felt but unresolved need for Azurity’s invention as of its filing date.

Azurity also argues that because enalapril was administered to children using compounding for so many years, this is evidence that a long-term stable formulation was not obvious, even if compounding had ceased by the time the present invention came about. This evidence consists of Dr. Mahan’s testimony that compounding was routinely used to administer enalapril to children even though it entailed safety risks. Because the obviousness inquiry must be “expansive and flexible,” KSR, 550 U.S. at 415, I have considered this evidence, but I find it less probative of nonobviousness because it predates the Epaned Kit’s patent and label. Even if Dr. Mahan’s testimony could show that a long-term stable enalapril liquid was nonobvious prior to the release

of the Epaned Kit, his testimony would not rebut evidence that the Epaned Kit made the claimed invention obvious. In particular, Dr. Mahan's testimony does not overcome Dr. Constantinides's detailed explanation showing how the composition and stability information disclosed in the '747 patent made it obvious how to develop a ready-to-use enalapril liquid. (See N.T. 286-90 (Constantinides)).²³

7. Determination of Obviousness

For the reasons set out above, and considering that secondary considerations of nonobviousness are only minimally probative, I find that Alkem has proven by clear and convincing evidence that the asserted claims would have been obvious to a POSA as of the filing date.²⁴

²³ The need Dr. Mahan identified is also not especially probative of nonobviousness because no testimony was offered tying the lack of a commercially available enalapril liquid to a lack of scientific know-how for making one—as opposed to it being unprofitable, burdened by regulation, not in demand, or difficult to monetize. (Cf. N.T. 559-60; Casas at 272 (“There are many factors that determine the lack of cost-effectiveness of this market of commercial pediatric oral liquid forms.”).) Azurity has thus not shown a “nexus” between the long-felt but unresolved need and the claimed invention. Fox Factory, 944 F.3d at 1373.

²⁴ Alkem further asks me to defer to the patent examiner's initial decision to reject the asserted claims for obviousness before ultimately allowing those claims based on evidence that different formulations—ones not using the claimed preservatives—were unexpectedly stable. Azurity objects because the PTO's reasons for initially denying the asserted claims are not in the record. “The basis (as opposed to the mere existence) of an examiner's initial finding of prima facie obviousness of an issued patent is . . . at most only one factual consideration that the trial court must consider in context of the totality of the evidence in determining whether the party asserting invalidity has met its statutory burden by clear and convincing evidence.” Pfizer v. Apotex, 480 F.3d at 1360. Alkem's post-trial brief identifies the examiner's initial rejection but provides little information about its basis. Because I find that the trial evidence constituted clear and convincing proof of obviousness, I need not consider what additional effect the examiner's initial rejection might have on that conclusion.

IV. WRITTEN DESCRIPTION

A. Facts Relevant to Written Description

The shared specification of the '482 and '621 patents describes enalapril liquid formulations based on their ingredients, pH, stability, and other characteristics. But, although every asserted claim requires that the liquid contain a preservative that is a paraben or mixture of parabens, the patents' shared specification does not contain a complete example of a liquid that uses only parabens as a preservative. (See N.T. 332-32 (Constantinides); N.T. 543 (Little).) Instead, liquids made using paraben preservatives can only be constructed by combining ingredients from separate places in the specification.

First, the specification describes a formulation with all of the claimed ingredients except for paraben preservatives:

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 5 ± 3 °C. for at least 12 months.

(Col. 3:39-48.) Second, the specification states that parabens can be used as the preservative, although it does not say which other ingredients these parabens should be combined with. (Col. 6:37-39.) Finally, with regard to the stability limitations, the specification states that “[t]he enalapril oral liquid formulations described herein are stable” under various definitions, some of which closely parallel the claim language and some of which are significantly less stringent (e.g., “for at least 1 month”). (Cols. 18:57-63, 19:15-20.)

Azurity's expert Dr. Little acknowledged that the specification does not contain “a disclosure of a formulation that meets all of the asserted claim limitations” of any asserted claim. (N.T.

543 (Little).) Dr. Little also testified that to find a paraben-containing stable combination from ingredients in the specification, a POSA would “mak[e] ... embodiments which are described in the specification and test[] them for stability.” (N.T. 469.)

The specification also contains six sections of “examples” of enalapril liquids identified as A, B, C, D, E, and G. (’621 patent, cols. 32-40.) Examples A through E contain data on the stability of those liquids. (See cols. 32-39.) Each example liquid contains at least one preservative that is not a paraben. (*Id.*; N.T. 332-32 (Constantinides).) Only Examples A and C describe liquids containing parabens, although these liquids also contain other preservatives, as well as other unclaimed ingredients such as mannitol and silicon dioxide. (’621 patent, cols. 32-34; N.T. 331-32 (Constantinides).) The specification contains stability data for these examples, none of which extends beyond 8 weeks of testing, and the specification does not state whether any of the example liquids would be stable for 12, 18, or 24 months.

B. Discussion

A patent must contain a written description that “clearly allow[s] persons of ordinary skill in the art to recognize that the inventor invented what is claimed.” Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (alterations and quotation marks omitted). “The essence of the written description requirement is that a patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention.” Nuvo Pharmaceuticals (Ireland) Designated Activity Co. v. Dr. Reddy’s Labs. Inc., 923 F.3d 1368, 1376 (Fed. Cir. 2019). “Requiring a written description of the invention limits patent protection to those who actually perform the difficult work of ‘invention’—that is, conceive of the complete and final invention with all its claimed

limitations—and disclose the fruits of that effort to the public.” Id. Therefore, “a description that merely renders the invention obvious does not satisfy the requirement[.]” Ariad Pharmaceuticals, 598 F.3d at 1351. And “[t]eaching how to make and use an invention does not necessarily satisfy the written description requirement.” Nuvo Pharmaceuticals, 923 F.3d at 1382.

“[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement.” Ariad Pharmaceuticals, 598 F.3d at 1352. “[W]ritten description is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described; it is not about whether the patentee has proven to the skilled reader that the invention works, or how to make it work, which is an enablement issue.” Alcon Research Ltd. v. Barr Labs., Inc., 745 F.3d 1180, 1191 (Fed. Cir. 2014). Thus, a lack of empirical data showing that described formulations meet all claim limitations does not mean that the claims lack written description. See id.

The claims at issue in this case use “functional language” to mark the boundaries of the claimed invention. See Ariad Pharmaceuticals, 598 F.3d at 1349. That is, Azurity does not claim ownership of all enalapril liquids made from water, buffers, sweeteners, and parabens—it only claims the subset of those liquids that are stable. The need for written description “is especially acute” when functional language is used. Id. In such a case, “the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.” Id. The specification can meet this standard by disclosing “either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.”

Id. at 1350. Alkem argues that the specification here does not meet this standard because a POSA reading the specification would not know which enalapril formulations containing parabens are as stable as the asserted claims require.

For the reasons that follow, I find that all asserted claims lack written description because the specification describes a large variety of ways to combine ingredients but does not say which combinations that use paraben preservatives are stable. That is, if a POSA were to combine ingredients from the specification, they would not know whether they would have the claimed invention.

Initially, Azurity is correct that aspects of the invention described separately in the specification can be combined to meet all limitations of the asserted claims. Those are: (1) ingredients other than parabens that appear in column 3; (2) parabens that appear in column 6; and (3) stability characteristics that are described in column 18. The difficulty is that the specification does not say whether any combination involving parabens meets the stability limitations. The specification lists many buffers, sweeteners, preservatives, and pHs that can be combined, but is largely silent on how these ingredients relate to stability. As Dr. Little acknowledged, a POSA seeking to determine which combinations involving parabens are stable would “mak[e] . . . embodiments . . . and test[] them for stability.” (N.T. 469 (Little).) Therefore, while a formulation meeting all claim limitations could theoretically be constructed by picking and choosing different parts of the specification, “a POSA is deprived of any meaningful guidance into what [formulations] beyond the examples and formulas, if any, would provide the” claimed stability. Idenix Pharmaceuticals LLC v. Gilead Sciences Inc., 941 F.3d 1149, 1164 (Fed. Cir. 2019). Because “the claimed invention does not appear in the specification,” the patents’ written description is inadequate. Ariad Pharmaceuticals, 598 F.3d at 1348.

Azurity also takes the position that it would have been simple for a POSA to determine

experimentally which combinations involving parabens are stable. Azurity's position is credible in light of my finding that a stable enalapril liquid with a paraben preservative was obvious even before Azurity's invention. But "a description that merely renders the invention obvious does not satisfy the written description requirement[.]" Ariad Pharmaceuticals, 598 F.3d at 1351. Because "one could not know which, if any, individual [variants] would yield [the claimed stability] without actually making and testing the variants," stable variants containing parabens are not adequately described. Novozymes A/S v. DuPont Nutrition Biosciences APS, 723 F.3d 1336, 1350 (Fed. Cir. 2013). The specification does not need to prove which paraben-containing formulations are stable or provide evidence that they are stable, but it does need to guide a reader to identify formulations meeting all claim limitations. Ariad Pharmaceuticals, 598 F.3d at 1348. The specification here does not provide the required guidance regarding which paraben-containing enalapril formulations are stable.

Azurity also references the stability testing data contained in the specification. But this data also fails to provide guidance as to which paraben-preserved formulations are stable. First, no example is preserved using only parabens: each contains at least one preservative that is not a paraben.²⁵ (N.T. 331-34 (Constantinides).) Second, the specification draws no conclusion that any tested formulations are stable. While I assume, given Alkem's burden and the lack of contrary evidence, that these short-term stability tests are valid, the specification does not identify any of

²⁵ Azurity points out that the asserted claims of the '482 patent may be construed to encompass formulations that contain multiple preservatives. But Dr. Little's concession that the specification does not disclose a formulation meeting all claim limitations implies that these examples differ from the claims. (See N.T. 543 (Little).) In any event, if the specification only describes how to make paraben formulations stable by mixing them with other preservatives, it does not describe formulations that (like the accused product in this case) use only paraben preservatives.

these examples as a stable, paraben-preserved liquid.

For the foregoing reasons, I find that Alkem has proven by clear and convincing evidence that the asserted claims are invalid for lack of written description.²⁶

V. CONCLUSION

For the reasons set out above, I conclude that Alkem's ANDA infringes all asserted claims. I also find that those claims are invalid for obviousness and lack of written description.

An appropriate order follows.

²⁶I do not reach Alkem's alternative argument that the asserted claims lack written description because the specification does not describe formulations using single-paraben preservatives.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC.,)	
)	
Plaintiff,)	
)	
v.)	C.A. No. 19-2100 (MSG)
)	
ALKEM LABORATORIES LTD.,)	
)	
Defendant.)	

PLAINTIFF AZURITY PHARMACEUTICALS, INC.'S NOTICE OF APPEAL

Pursuant to Federal Rule of Appellate Procedure 3(a), notice is hereby given that Plaintiff Azurity Pharmaceuticals, Inc. ("Azurity"), appeals to the United States Court of Appeals for the Federal Circuit from this Court's Order and Judgment (D.I. 214) entered on February 10, 2023, and any and all other orders, opinions, rulings, findings, or conclusions adverse to Azurity, including the Memorandum Opinion (D.I. 213) issued on February 10, 2023.

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February 14, 2023

CERTIFICATE OF SERVICE

I hereby certify that on February 14, 2023, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on February 14, 2023, upon the following in the manner indicated:

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U.S. District Court
District of Delaware (Wilmington)
CIVIL DOCKET FOR CASE #: 1:19-cv-02100-MSG

Azurity Pharmaceuticals, Inc. v. Alkem Laboratories Ltd.

Assigned to: Judge Mitchell S. Goldberg

Related Cases: [1:18-cv-01962-MSG](#)[1:19-cv-00678-LPS](#)[1:19-cv-01067-MSG](#)[1:20-cv-00753-LPS](#)[1:21-cv-01286-MSG](#)[1:21-cv-01707-MSG](#)[1:21-cv-01455-MSG](#)[1:21-cv-00196-MSG](#)[1:20-cv-01256-MSG](#)[1:20-cv-01255-LPS](#)

Date Filed: 11/05/2019

Date Terminated: 02/10/2023

Jury Demand: None

Nature of Suit: 835 Patent - Abbreviated

New Drug Application(ANDA)

Jurisdiction: Federal Question

Case in other court: USCA for the Federal Circuit, 23-01540

Cause: 35:1 Patent Infringement

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ATTORNEY TO BE NOTICED

Date Filed	#	Docket Text
11/05/2019	1	COMPLAINT for patent infringement filed against Alkem Laboratories Ltd. - Magistrate Consent Notice to Pltf. (Filing fee \$ 400, receipt number 0311-2771746.) - filed by Silvergate Pharmaceuticals, Inc.. (Attachments: # 1 Exhibit A-D, # 2 Civil Cover Sheet) (sam) (Entered: 11/06/2019)
11/05/2019	2	Notice, Consent and Referral forms re: U.S. Magistrate Judge jurisdiction. (sam) (Entered: 11/06/2019)
11/05/2019	3	Supplemental information for patent cases involving an Abbreviated New Drug Application (ANDA) - Date Patentee(s) Received Notice: September 25, 2019. Date of Expiration of Patent: March 25, 2036.Thirty Month Stay Deadline: 03/25/2022. (sam) (Entered: 11/06/2019)
11/05/2019	4	Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s) 9,669,008 B1 ;9,808,442 B2 ;10,039,745 B2 ;10,154,987 B2. (sam) (Entered: 11/06/2019)
11/05/2019	5	Disclosure Statement pursuant to Rule 7.1: identifying Corporate Parent CutisPharma, Inc. for Silvergate Pharmaceuticals, Inc. filed by Silvergate Pharmaceuticals, Inc. (sam) (Entered: 11/06/2019)
11/06/2019		Summons Issued with Magistrate Consent Notice attached as to Alkem Laboratories Ltd. on 11/6/2019. Requesting party or attorney should pick up issued summons at the Help Desk, Room 4209, or call 302-573-6170 and ask the Clerk to mail the summons to them. (sam) (Entered: 11/06/2019)
11/13/2019		Case Assigned to Judge Leonard P. Stark. Please include the initials of the Judge (LPS) after the case number on all documents filed. (rjb) (Entered: 11/13/2019)
11/14/2019	6	MOTION for Pro Hac Vice Appearance of Attorney Wendy L. Devine, Kristina M. Hanson, Yan-Xin Li, and Natalie J. Morgan - filed by Silvergate Pharmaceuticals, Inc. (Dellinger, Megan) Modified on 1/29/2020 (ntl). (Entered: 11/14/2019)
11/15/2019		SO ORDERED, re (11 in 1:19-cv-01067-LPS, 6 in 1:19-cv-02100-LPS) MOTION for Pro Hac Vice Appearance of Attorney Wendy L. Devine, Kristina M. Hanson, Yan-Xin Li, and Natalie J. Morgan filed by Silvergate Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 11/15/19. Associated Cases: 1:19-cv-01067-LPS, 1:19-cv-02100-LPS (ntl) Modified on 1/29/2020 (ntl). (Entered: 11/15/2019)
01/09/2020	7	MOTION for Pro Hac Vice Appearance of Attorney Talin Gordnia - filed by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 01/09/2020)
01/10/2020		SO ORDERED, re (38 in 1:19-cv-00678-LPS, 48 in 1:18-cv-01962-LPS, 36 in 1:19-cv-01067-LPS, 7 in 1:19-cv-02100-LPS) MOTION for Pro Hac Vice Appearance of Attorney Talin Gordnia filed by Silvergate Pharmaceuticals, Inc. Signed by Judge

		Leonard P. Stark on 1/10/2020. Associated Cases: 1:18-cv-01962-LPS, 1:19-cv-00678-LPS, 1:19-cv-01067-LPS, 1:19-cv-02100-LPS (ntl) (Entered: 01/10/2020)
01/28/2020	8	AFFIDAVIT of Service for Summons, Complaint and related papers served on Alkem Laboratories Ltd. on January 28, 2020, filed by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 01/28/2020)
01/29/2020		Pro Hac Vice Attorney Wendy L. Devine for Silvergate Pharmaceuticals, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (mal) (Entered: 01/29/2020)
01/29/2020		Pro Hac Vice Attorney Yan-Xin Li for Silvergate Pharmaceuticals, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (mal) (Entered: 01/29/2020)
01/29/2020		Pro Hac Vice Attorney Natalie J. Morgan for Silvergate Pharmaceuticals, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (mal) (Entered: 01/29/2020)
02/03/2020		Pro Hac Vice Attorney Talin Gordnia for Silvergate Pharmaceuticals, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (kmd) (Entered: 02/03/2020)
02/20/2020	9	ANSWER to 1 Complaint, by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 02/20/2020)
02/20/2020	10	Disclosure Statement pursuant to Rule 7.1: No Parents or Affiliates Listed filed by Alkem Laboratories Ltd.. (Dorsney, Kenneth) (Entered: 02/20/2020)
05/05/2020	11	MOTION for Pro Hac Vice Appearance of Attorney George J. Barry III and Attorney Timothy H. Kratz - filed by Alkem Laboratories Ltd.. (Dorsney, Kenneth) (Entered: 05/05/2020)
05/05/2020		SO ORDERED, re 11 MOTION for Pro Hac Vice Appearance of Attorney George J. Barry III and Attorney Timothy H. Kratz filed by Alkem Laboratories Ltd. Signed by Judge Leonard P. Stark on 5/5/20. (ntl) (Entered: 05/05/2020)
05/08/2020		Pro Hac Vice Attorneys George J. Barry, III and Timothy H. Kratz for Alkem Laboratories Ltd. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (kmd) (Entered: 05/08/2020)
08/03/2020	12	Letter to The Honorable Leonard P. Stark from Kenneth L. Dorsney regarding request for a Rule 16(b) Scheduling Conference. (Dorsney, Kenneth) (Entered: 08/03/2020)
09/11/2020	13	ORAL ORDER: Having reviewed the parties' August 3, 2020 letter (D.I. 12), IT IS HEREBY ORDERED that the Court will hold a scheduling conference on September 25, 2020 at 3:00 p.m. The parties shall meet and confer and submit a proposed scheduling order no later than September 21, 2020. The parties shall use the following dial-in information: 877-336-1829 and access code 1408971. ORDERED by Judge Leonard P. Stark on 9/11/20. (ntl) (Entered: 09/11/2020)
09/18/2020		Pro Hac Vice Attorney Kristina M. Hanson for Silvergate Pharmaceuticals, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the

		registered users of CM/ECF and shall be required to file all papers. (mal) (Entered: 09/18/2020)
09/21/2020	14	PROPOSED ORDER Scheduling Order by Silvergate Pharmaceuticals, Inc.. (Attachments: # 1 Letter to Judge Stark)(Dellinger, Megan) (Entered: 09/21/2020)
09/23/2020	15	SCHEDULING ORDER: Case referred to the Magistrate Judge for the purpose of exploring ADR. Fact Discovery completed by 5/7/2021. Status Report due by 3/31/2021. Joint Claim Construction Brief due by 3/23/2021. A Markman Hearing is set for 4/5/2021 at 09:00 AM in Courtroom 6B before Judge Leonard P. Stark. Proposed Pretrial Order due by 12/30/2021. A Final Pretrial Conference is set for 1/7/2022 at 11:30 AM in Courtroom 6B before Judge Leonard P. Stark. A 5-day Bench Trial is set for 1/24/2022 at 08:30 AM in Courtroom 6B before Judge Leonard P. Stark. Signed by Judge Leonard P. Stark on 9/23/20. (ntl) (Entered: 09/23/2020)
09/23/2020	16	ORAL ORDER: IT IS HEREBY ORDERED that the teleconference scheduled for September 25 is CANCELLED. ORDERED by Judge Leonard P. Stark on 9/23/20. (ntl) (Entered: 09/23/2020)
09/24/2020		CASE REFERRED to Magistrate Judge Christopher J. Burke for Mediation. Please see Standing Order dated January 20, 2016, regarding disclosure of confidential ADR communications. A link to the standing order is provided here for your convenience at https://www.ded.uscourts.gov/sites/ded/files/forms/StandingOrderforADR-Mediation.pdf (cak) (Entered: 09/24/2020)
09/24/2020	17	ORAL ORDER: If during the history of this case, Plaintiff(s) and Defendant(s) jointly wish to schedule a form of alternative dispute resolution ("ADR"), such as mediation, with Judge Burke, they should contact chambers by e-mail at Deborah_Benyo@ded.uscourts.gov or by phone. Additionally, if either side wishes to speak ex parte with Judge Burke regarding ADR matters, they may contact chambers via e-mail or by phone to arrange a time for a call. Ordered by Judge Christopher J. Burke on 9/24/2020. (dlb) (Entered: 09/24/2020)
09/30/2020	18	NOTICE OF SERVICE of Initial Disclosures Pursuant to Rule 26(a)(1) filed by Silvergate Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 09/30/2020)
09/30/2020	19	NOTICE OF SERVICE of Alkem's Rule 26(a)(1) Initial Disclosures filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 09/30/2020)
10/01/2020	20	NOTICE OF SERVICE of Plaintiff Silvergate Pharmaceuticals Inc.'s Initial Disclosures Pursuant to Paragraph 3 of the Delaware Default Standard for Discovery filed by Silvergate Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 10/01/2020)
10/01/2020	21	NOTICE OF SERVICE of Alkem's Paragraph 3 Disclosures filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 10/01/2020)
10/08/2020	22	NOTICE OF SERVICE of Plaintiff Silvergate Pharmaceuticals, Inc.'s Identification of Accused Products and Asserted Patents Pursuant to Paragraph 4.a of the Delaware Default Standard for Discovery filed by Silvergate Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 10/08/2020)
10/15/2020	23	PROPOSED ORDER Stipulated Protective Order by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 10/15/2020)
10/20/2020		SO ORDERED, re 23 Stipulated Protective Order filed by Silvergate Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 10/19/20. (ntl) (Entered: 10/20/2020)
10/30/2020	24	STIPULATION TO EXTEND TIME for Production of Core Technical Documents and Plaintiff's Initial Infringement Contentions to November 24, 2020 and December 22,

		2020 - filed by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 10/30/2020)
10/30/2020		SO ORDERED, re 24 STIPULATION TO EXTEND TIME for Production of Core Technical Documents and Plaintiff's Initial Infringement Contentions to November 24, 2020 and December 22, 2020 filed by Silvergate Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 10/30/20. (ntl) (Entered: 10/30/2020)
11/24/2020	25	NOTICE OF SERVICE of Alkem's Core Technical Documents filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 11/24/2020)
12/22/2020	26	NOTICE OF SERVICE of Initial Infringement Claim Charts filed by Silvergate Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 12/22/2020)
01/08/2021	27	Joint MOTION Requesting New Markman Hearing Date and Amending the Case Schedule - filed by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 01/08/2021)
01/13/2021	28	SO ORDERED, re 27 Joint MOTION Requesting New Markman Hearing Date and Amending the Case Schedule -- Fact Discovery completed by 6/14/2021. Joint Claim Construction Brief due by 4/29/2021. Status Report due by 3/31/2021. A Markman Hearing is set for 5/20/2021 at 04:00 PM before Judge Leonard P. Stark. Signed by Judge Leonard P. Stark on 1/11/21. (ntl) (Entered: 01/13/2021)
02/18/2021	29	NOTICE OF SERVICE of Alkem's Initial Invalidity Contentions filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 02/18/2021)
02/19/2021	30	NOTICE OF SERVICE of (1) Plaintiff Silvergate Pharmaceuticals, Inc.'s First Set of Common Interrogatories (Nos. 1-10); and (2) Plaintiff Silvergate Pharmaceuticals, Inc.'s First Set of Requests for Production (Nos. 1-64) filed by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 02/19/2021)
02/25/2021	31	NOTICE OF SERVICE of Plaintiff Silvergate Pharmaceuticals, Inc.'s Disclosure of Proposed Claim Terms and Constructions for U.S. Patent Nos. 9,669,008, 9,808,442, 10,039,745, 10,154,987, 10,772,868, 10,786,482, and 10,918,621 filed by Silvergate Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 02/25/2021)
03/04/2021	32	CLAIM Construction Chart by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 03/04/2021)
03/23/2021	33	Joint STIPULATION TO EXTEND TIME regarding certain claim construction deadlines to various dates - filed by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 03/23/2021)
03/25/2021		SO ORDERED, re 33 Joint STIPULATION TO EXTEND TIME regarding certain claim construction deadlines to various dates filed by Silvergate Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 3/24/21. (ntl) (Entered: 03/25/2021)
03/31/2021	34	STIPULATION TO EXTEND TIME for the parties to file an interim status report to April 7, 2021 - filed by Alkem Laboratories Ltd.. (Dorsney, Kenneth) (Entered: 03/31/2021)
04/01/2021	35	Interim STATUS REPORT by Alkem Laboratories Ltd.. (Dorsney, Kenneth) (Entered: 04/01/2021)
04/06/2021		SO ORDERED, re 34 STIPULATION TO EXTEND TIME for the parties to file an interim status report to April 7, 2021 filed by Alkem Laboratories Ltd. Signed by Judge Leonard P. Stark on 4/5/21. (ntl) (Entered: 04/06/2021)

04/08/2021	36	STIPULATION and [Proposed] Order to File First Amended Complaint by Silvergate Pharmaceuticals, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2)(Dellinger, Megan) (Entered: 04/08/2021)
04/08/2021	37	Joint MOTION to Amend the Case Schedule and Set a New Trial Date - filed by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 04/08/2021)
04/13/2021	38	SO ORDERED, re 37 Joint MOTION to Amend the Case Schedule and Set a New Trial Date filed by Silvergate Pharmaceuticals, Inc. -- Fact Discovery completed by 10/5/2021. Joint Claim Construction Brief due by 7/23/2021. Proposed Pretrial Order due by 3/18/2022. Status Report due by 9/9/2021. A 5-day Bench Trial is set for 4/4/2022 at 08:30 AM in Courtroom 6B before Judge Leonard P. Stark. A Final Pretrial Conference is set for 3/25/2022 at 09:00 AM in Courtroom 6B before Judge Leonard P. Stark. A Markman Hearing is set for 8/23/2021 at 09:00 AM before Judge Leonard P. Stark. Signed by Judge Leonard P. Stark on 4/8/21. (ntl) (Entered: 04/13/2021)
04/13/2021		SO ORDERED, re 36 STIPULATION and [Proposed] Order to File First Amended Complaint filed by Silvergate Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 4/8/21. (ntl) (Entered: 04/13/2021)
04/13/2021	39	First AMENDED COMPLAINT against Alkem Laboratories Ltd.- filed by Silvergate Pharmaceuticals, Inc.. (Attachments: # 1 Exhibits A-G)(Dellinger, Megan) (Entered: 04/13/2021)
04/13/2021	40	Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s) 9,669,008 ;9,808,442 ;10,039,745 ;10,154,987 ;10,772,868 ;10,786,482 ;10,918,621 . (Dellinger, Megan) (Entered: 04/13/2021)
04/20/2021	41	ANSWER to Amended Complaint, re: 39 Amended Complaint by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 04/20/2021)
04/22/2021	42	NOTICE OF SERVICE of (1) Plaintiff Silvergate Pharmaceuticals, Inc.'s Amended Initial Disclosures Pursuant to Paragraph 3 of the Delaware Default Standard for Discovery; (2) Plaintiff Silvergate Pharmaceuticals, Inc.'s Amended Identification of Accused Products and Asserted Patents Pursuant to Paragraph 4.a of the Delaware Default Standard for Discovery; (3) Plaintiff Silvergate Pharmaceuticals, Inc.'s Amended Initial Disclosures Pursuant to Rule 26(a)(1); and (4) Plaintiff Silvergate Pharmaceuticals, Inc.'s Initial Infringement Claim Charts filed by Silvergate Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 04/22/2021)
04/22/2021	43	NOTICE OF SERVICE of (1) Alkem's response to Plaintiff's First Set of Common Interrogatories (Nos. 1-10); and (2) Alkem's response to Plaintiff's First Set of Requests for Production (Nos. 1-64) filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 04/22/2021)
04/28/2021	44	NOTICE OF SERVICE of First set of requests for production filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 04/28/2021)
05/07/2021	45	NOTICE OF SERVICE of Defendant Alkem Laboratories Ltd.'s Initial Invalidity Contentions regarding U.S. Patent Nos. 10,772,868 B2; 10,918,621 B2; and 10,786,482 B2 filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 05/07/2021)
05/13/2021	46	NOTICE OF SERVICE of Alkem's Identification of Claim Terms and Constructions for U.S. Patent Nos. 10,772,868 B2; 10,918,621 B2; and 10,786,482 B2 filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 05/13/2021)
05/18/2021	47	STIPULATION and [Proposed] Order Regarding Certain Claim Construction Deadlines and Foregoing Technology Tutorials by Silvergate Pharmaceuticals, Inc.. (Dellinger,

		Megan) (Entered: 05/18/2021)
05/20/2021		SO ORDERED, re 47 STIPULATION and [Proposed] Order Regarding Certain Claim Construction Deadlines and Foregoing Technology Tutorials -- Joint Claim Construction Brief due by 7/30/2021. Signed by Judge Leonard P. Stark on 5/20/21. (ntl) (Entered: 05/20/2021)
05/21/2021	48	MOTION to Intervene <i>for purposes of filing a motion for protective order to protect Third Party Bionpharma's sealed confidential information</i> - filed by Bionpharma Inc.. (Attachments: # 1 Proposed Order, # 2 7.1.1. Statement)(Phillips, John) (Entered: 05/21/2021)
05/21/2021	49	MEMORANDUM in Support re 48 MOTION to Intervene <i>for purposes of filing a motion for protective order to protect Third Party Bionpharma's sealed confidential information</i> filed by Bionpharma Inc.. Answering Brief/Response due date per Local Rules is 6/4/2021. (Attachments: # 1 Exhibit A)(Phillips, John) (Entered: 05/21/2021)
05/25/2021	50	STIPULATION and [Proposed] Order Regarding Joint Claim Construction Chart Deadline by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 05/25/2021)
05/26/2021	51	CLAIM Construction Chart by Silvergate Pharmaceuticals, Inc.. (Attachments: # 1 Exhibits A-C)(Dellinger, Megan) (Entered: 05/26/2021)
05/27/2021		SO ORDERED, re 50 STIPULATION and [Proposed] Order Regarding Joint Claim Construction Chart Deadline filed by Silvergate Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 5/27/21. (ntl) (Entered: 05/27/2021)
06/02/2021	52	NOTICE OF SERVICE of Plaintiff Silvergate Pharmaceuticals, Inc.'s Objections and Response to Defendant Alkem Laboratories Ltd.'s First Set of Requests for the Production of Documents and Things (No. 1) filed by Silvergate Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 06/02/2021)
06/04/2021	53	STIPULATION TO EXTEND TIME Opposition to Motion to Intervene to June 18, 2021 - filed by Alkem Laboratories Ltd.. (Hitch, Cortlan) (Entered: 06/04/2021)
06/04/2021	54	STATEMENT re 48 MOTION to Intervene <i>for purposes of filing a motion for protective order to protect Third Party Bionpharma's sealed confidential information -- Plaintiff's Statement of Non-Opposition</i> -- by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 06/04/2021)
06/08/2021	55	NOTICE OF SERVICE of Opening Claim Construction Brief for U.S. Patent Nos. 10,722,868; 10,786,482; and 10,918,621 filed by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 06/08/2021)
06/09/2021	56	NOTICE requesting Clerk to remove Yan-Xin Li as co-counsel.. (Dellinger, Megan) (Entered: 06/09/2021)
06/10/2021		SO ORDERED, re (30 in 1:21-cv-00196-LPS, 33 in 1:20-cv-00753-LPS, 53 in 1:19-cv-02100-LPS) STIPULATION TO EXTEND TIME Opposition to Motion to Intervene to June 18, 2021 filed by Alkem Laboratories Ltd. Signed by Judge Leonard P. Stark on 6/10/21. Associated Cases: 1:19-cv-02100-LPS, 1:20-cv-00753-LPS, 1:21-cv-00196-LPS (ntl) (Entered: 06/10/2021)
06/10/2021	57	MOTION to Substitute Party: Azurity Pharmaceuticals, Inc. to replace Silvergate Pharmaceuticals, Inc. - filed by Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 06/10/2021)
06/10/2021	58	STIPULATION Regarding Bionpharma Intervention by Alkem Laboratories Ltd.. (Hitch, Cortlan) (Entered: 06/10/2021)

06/11/2021	59	ORAL ORDER: Having reviewed the parties' various submissions in the Alkem matter (C.A. No. 19-2100), the parties' proposed stipulation (D.I. 58) is SO ORDERED. The pending Motion to Intervene (D.I. 48) is GRANTED to the extent set forth in the stipulation (D.I. 58). IT IS FURTHER ORDERED that the parties' unopposed motion to substitute Azurity Pharmaceuticals, Inc. for Silvergate (D.I. 57) is GRANTED. ORDERED by Judge Leonard P. Stark on 6/11/21. (ntl) (Entered: 06/11/2021)
06/16/2021	60	NOTICE of Appearance by John C. Phillips, Jr on behalf of Bionpharma Inc. (Phillips, John) (Entered: 06/16/2021)
06/16/2021	61	NOTICE of Appearance by Megan C. Haney on behalf of Bionpharma Inc. (Haney, Megan) (Entered: 06/16/2021)
06/29/2021	62	STIPULATION to Amend Schedule for Claim Construction Briefing by Alkem Laboratories Ltd.. (Hitch, Cortlan) (Entered: 06/29/2021)
06/30/2021		SO ORDERED, re 62 STIPULATION and Order to Amend Schedule for Claim Construction Briefing filed by Alkem Laboratories Ltd. Signed by Judge Leonard P. Stark on 6/30/21. (ntl) (Entered: 06/30/2021)
07/02/2021	63	Letter to The Honorable Leonard P. Stark from Kenneth L. Dorsney regarding status of protective order dispute - re 58 Stipulation, 59 Order,. (Dorsney, Kenneth) (Entered: 07/02/2021)
07/08/2021	64	STIPULATION Regarding Production of Intervenor Bionpharma's Confidential Information by Alkem Laboratories Ltd.. (Hitch, Cortlan) (Entered: 07/08/2021)
07/09/2021		SO ORDERED, re 64 STIPULATION Regarding Production of Intervenor Bionpharma's Confidential Information by Alkem Laboratories Ltd.. Signed by Judge Leonard P. Stark on 7/9/2021. (etg) (Entered: 07/09/2021)
07/12/2021	65	STIPULATION to extend time for Alkem Laboratories Ltd. to serve its answering claim construction brief and for the parties to meet and confer to submit a revised proposed schedule by Alkem Laboratories Ltd.. (Dorsney, Kenneth) (Entered: 07/12/2021)
07/13/2021		SO ORDERED, re 65 STIPULATION to extend time for Alkem Laboratories Ltd. to serve its answering claim construction brief and for the parties to meet and confer to submit a revised proposed schedule. Signed by Judge Leonard P. Stark on 7/13/21. (ntl) (Entered: 07/13/2021)
07/16/2021	66	NOTICE OF SERVICE of Defendant Alkem Laboratories Ltd.'s Answering Claim Construction Brief for U.S. Patent Nos. 10,772,868; 10,786,482; and 10,918,621 filed by Alkem Laboratories Ltd..(Hitch, Cortlan) (Entered: 07/16/2021)
07/21/2021	67	[SEALED] STIPULATION Regarding Claim Construction Briefing Schedule by Alkem Laboratories Ltd.. (Hitch, Cortlan) (Entered: 07/21/2021)
07/22/2021		SO ORDERED, re 67 [SEALED] STIPULATION Regarding Claim Construction Briefing Schedule filed by Alkem Laboratories Ltd. Signed by Judge Leonard P. Stark on 7/22/21. (ntl) (Entered: 07/22/2021)
07/22/2021	68	ORAL ORDER: Having reviewed the parties' stipulation (D.I. 67), and the parties having expressed no preference on the format for the upcoming claim construction hearing, IT IS HEREBY ORDERED that the claim construction hearing on August 23 will be held remotely by videoconference. It will begin at 4:30 p.m. No later than August 20 at 4:00 p.m. the parties shall provide chambers with (i) the necessary information for it to connect to the hearing and (ii) a copy of any slides or demonstratives to which they may refer during the hearing. At the same time, the parties shall docket a public letter providing the necessary information to allow any member of the public to attend the

		hearing without having the ability to speak or interrupt the proceedings. ORDERED by Judge Leonard P. Stark on 7/22/21. (ntl) (Entered: 07/22/2021)
07/28/2021	69	REDACTED VERSION of 67 Stipulation regarding claim construction briefing schedule by Alkem Laboratories Ltd.. (Hitch, Cortlan) (Entered: 07/28/2021)
07/29/2021	70	NOTICE OF SERVICE of Plaintiff Azurity Pharmaceuticals, Inc.'s Reply Claim Construction Brief for U.S. Patent Nos. 10,722,868; 10,786,482; and 10,918,621 filed by Azurity Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 07/29/2021)
08/05/2021	71	NOTICE OF SERVICE of Defendant Alkem Laboratories Ltd.'s Sur-Reply Claim Construction Brief for U.S. Patent Nos. 10,772,868; 10,786,482; and 10,918,621 filed by Alkem Laboratories Ltd..(Hitch, Cortlan) (Entered: 08/05/2021)
08/09/2021	72	[SEALED] JOINT CLAIM CONSTRUCTION BRIEF filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 08/09/2021)
08/09/2021	73	APPENDIX re 72 Joint Claim Construction Brief by Azurity Pharmaceuticals, Inc.. (Attachments: # 1 Exhibit A-B)(Dellinger, Megan) (Entered: 08/09/2021)
08/09/2021	74	Letter to The Honorable Leonard P. Stark from Megan E. Dellinger regarding Markman Hearing Scheduled for August 23, 2021. (Dellinger, Megan) (Entered: 08/09/2021)
08/12/2021	75	REDACTED VERSION of 72 Joint Claim Construction Brief by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 08/12/2021)
08/16/2021	76	ORAL ORDER: IT IS HEREBY ORDERED that the Markman Hearing on August 23, 2021 will begin at 5:00 p.m. and each side will be allocated up to forty-five (45) minutes for argument. ORDERED by Judge Leonard P. Stark on 8/16/21. (ntl) (Entered: 08/16/2021)
08/17/2021	77	MOTION for Pro Hac Vice Appearance of Attorney T.O. Kong - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 08/17/2021)
08/18/2021		SO ORDERED, re 77 MOTION for Pro Hac Vice Appearance of Attorney T.O. Kong filed by Azurity Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 8/18/21. (ntl) (Entered: 08/18/2021)
08/19/2021	78	ORAL ORDER: IT IS HEREBY ORDERED that the Markman hearing on August 23, 2021 is available to the public using the following dial-in for audio access: 1-855- 747-8824 Passcode: 8975254786. Audio reproduction of the proceeding is strictly prohibited. ORDERED by Judge Leonard P. Stark on 8/19/21. (ntl) (Entered: 08/19/2021)
08/23/2021		Minute Entry for proceedings held before Judge Leonard P. Stark - Markman Hearing held (by video) on 8/23/2021. (Court Reporter B. Gaffigan.) (ntl) (Entered: 08/24/2021)
08/30/2021	79	Official Transcript of Claim Construction Hearing held on August 23, 2021 before Judge Leonard P. Stark. Court Reporter Brian Gaffigan email: gaffigan@verizon.net. Transcript may be viewed at the court public terminal or ordered/purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 9/20/2021. Redacted Transcript Deadline set for 9/30/2021. Release of Transcript Restriction set for 11/29/2021. (bpg) (Entered: 08/30/2021)
08/31/2021	80	NOTICE OF SERVICE of Alkem's First Supplemental Responses to Azurity's First Set of Common Interrogatories (Nos. 2-5, 7 and 9) filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 08/31/2021)
09/02/2021	81	Joint MOTION for Extension of Time to <i>Set New Trial Date and Amend Case Schedule</i> -

		filed by Alkem Laboratories Ltd.. (Hitch, Cortlan) (Entered: 09/02/2021)
09/09/2021	82	STIPULATION TO EXTEND TIME for the parties to submit a joint status report to September 16, 2021 - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 09/09/2021)
09/10/2021		SO ORDERED, re 82 STIPULATION TO EXTEND TIME for the parties to submit a joint status report to September 16, 2021 filed by Azurity Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 9/10/21. (ntl) (Entered: 09/10/2021)
09/14/2021	83	SO ORDERED, re 81 Joint MOTION to Amend the Case Schedule and Set a New Trial Date -- Fact Discovery completed by 2/10/2022. Proposed Pretrial Order due by 7/22/2022. Status Report due by 1/12/2022. A 5-day Bench Trial is set for 8/8/2022 at 08:30 AM in Courtroom 6B before Judge Leonard P. Stark. A Final Pretrial Conference is set for 7/29/2022 at 04:00 PM in Courtroom 6B before Judge Leonard P. Stark. Signed by Judge Leonard P. Stark on 9/14/21. (ntl) (Entered: 09/14/2021)
09/20/2021	84	Letter to The Honorable Leonard P. Stark from Megan E. Dellinger regarding request for discovery teleconference. (Dellinger, Megan) (Entered: 09/20/2021)
10/08/2021	85	ORAL ORDER: IT IS HEREBY ORDERED that this case is referred to Magistrate Judge Christopher J. Burke to hear and resolve all pre-trial matters up to and including expert discovery matters (but not including summary judgment motions, Daubert motions, pre-trial motions in limine or the pre-trial conference), subject to 28 U.S.C. § 636(b) and any further Order of the Court. ORDERED by Judge Leonard P. Stark on 10/8/21. (ntl) (Entered: 10/08/2021)
10/12/2021		Remark: The parties should be aware that the Court encourages the participation of newer attorneys in courtroom proceedings and at oral argument. Please see the Court's Standing Order Regarding Courtroom Opportunities for Newer Attorneys, a link to which is provided here for the parties' convenience: http://www.ded.uscourts.gov/sites/ded/files/forms/StandingOrder2017.pdf (mlc) (Entered: 10/12/2021)
10/12/2021		Remark: The parties should follow the Court's Standing Order Regarding Courtesy Copies, a copy of which is found on Judge Burke's portion of the District Court's webpage: https://www.ded.uscourts.gov/judge/magistrate-judge-christopher-j-burke (mlc) (Entered: 10/12/2021)
10/12/2021	86	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' September 20, 2021 letter requesting a discovery dispute teleconference regarding one discovery dispute. (D.I. 84) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is set for 11/8/2021 at 01:00 PM before Judge Christopher J. Burke.; (3) On October 19, 2021, any party seeking relief shall file with the Court a letter, not to exceed two (2) single-spaced pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. On October 26, 2021, any party opposing the application for relief may file a letter, not to exceed two (2) single-spaced pages, in no less than 12-point font, outlining that party's reasons for its opposition.; (4) The parties should also consult Judge Burke's "Guidelines for Discovery Disputes," which is found in the "Guidelines" tab on Judge Burke's portion of the District Court's website.; (5) By no later than November 3, 2021, the parties shall jointly provide the Court's Courtroom Deputy, Ms. Benyo, with a dial-in number via e-mail to use for the call.; and (6) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the

		conference. Ordered by Judge Christopher J. Burke on 10/12/2021. (mlc) (Entered: 10/12/2021)
10/12/2021	87	ORAL ORDER: The Court, having reviewed the case history in light of the October 8, 2021 referral, hereby ORDERS that the procedures for resolving a dispute relating to discovery or the protective order set out in the Scheduling Order, (D.I. 15 at 7-8), will be modified as follows: Should counsel find, after good faith efforts including verbal communication among Delaware and Lead Counsel for all parties to the dispute, that they are unable to resolve a discovery or protective order matter, the parties involved in the dispute shall submit a joint letter with the text set out in the Court's standard Rule 16 Scheduling Order for Patent cases, which can be found in the "Forms" tab of Magistrate Judge Burke's page on the District Court's website. For disputes relating to discovery, the moving party (i.e., the party seeking relief from the Court) should also file a Motion For Teleconference To Resolve Discovery Dispute, and for disputes relating to protective orders, the parties shall file a Joint Motion for Teleconference to Resolve Protective Order Dispute. The suggested text for these motions can be found in the same Forms tab. The Court will thereafter set a discovery or protective order dispute telephone conference and letter briefing schedule. Ordered by Judge Christopher J. Burke on 10/12/2021. (mlc) (Entered: 10/12/2021)
10/13/2021	88	ORAL ORDER: IT IS HEREBY ORDERED that the Referral Order at D.I. 85 is WITHDRAWN. IT IS FURTHER ORDERED that this case is referred to Magistrate Judge Christopher J. Burke, pursuant to 28 U.S.C. § 636(b), to hear and resolve all discovery disputes (including D.I. 84). ORDERED by Judge Leonard P. Stark on 10/13/21. (ntl) (Entered: 10/13/2021)
10/19/2021	89	MOTION for Teleconference to Resolve Discovery Dispute - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 10/19/2021)
10/19/2021	90	[SEALED] Letter to The Honorable Christopher J. Burke from Megan E. Dellinger regarding discovery dispute. (Attachments: # 1 Text of Proposed Order, # 2 Exhibits A-I) (Dellinger, Megan) (Entered: 10/19/2021)
10/25/2021	91	Remark: The Court recognizes that it is now more than 60 days since the claim construction hearing. The Court currently anticipates issuing its order regarding claim construction by on or around November 22. (ntl) (Entered: 10/25/2021)
10/26/2021	92	Letter to The Honorable Christopher J. Burke from Kenneth L. Dorsney regarding Response to Discovery Dispute Letter - re 90 Letter. (Dorsney, Kenneth) (Entered: 10/26/2021)
10/26/2021	93	STIPULATION TO EXTEND TIME for plaintiff to file a redacted version of its letter regarding a discovery dispute to November 2, 2021 - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 10/26/2021)
10/27/2021		SO ORDERED D.I. 93 STIPULATION TO EXTEND TIME for plaintiff to file a redacted version of its letter regarding a discovery dispute to November 2, 2021 filed by Azurity Pharmaceuticals, Inc. Ordered by Judge Christopher J. Burke on 10/27/2021. (dlb) (Entered: 10/27/2021)
11/01/2021	94	REDACTED VERSION of 90 Letter by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 11/01/2021)
11/02/2021	95	PROPOSED ORDER re 90 Letter by Azurity Pharmaceuticals, Inc.. (Attachments: # 1 Letter to The Honorable Christopher J. Burke)(Dellinger, Megan) (Entered: 11/02/2021)
11/04/2021	96	MOTION for Pro Hac Vice Appearance of Attorney Nicholas Halkowski - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 11/04/2021)

11/05/2021		SO ORDERED, re 96 MOTION for Pro Hac Vice Appearance of Attorney Nicholas Halkowski filed by Azurity Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 11/5/21. (ntl) (Entered: 11/05/2021)
11/08/2021		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery Conference held on 11/8/2021. The Court heard argument from the parties regarding the discovery dispute motion. (D.I. 89) The Court resolved the parties' disputes. The transcript shall serve as the substance of the Court's order. (Court Reporter Stacy Vickers (Hawkins). Clerk: M. Crawford) Appearances: M. Dellinger, T. Kong and N. Halkowski for Plaintiff; C. Hitch and T. Kratzfor Defendant. (mlc) (Entered: 11/08/2021)
11/16/2021	97	MEMORANDUM OPINION re claim construction. Signed by Judge Leonard P. Stark on 11/16/21. (ntl) (Entered: 11/16/2021)
11/16/2021	98	ORDER re 97 Memorandum Opinion regarding claim construction. Signed by Judge Leonard P. Stark on 11/16/21. (ntl) (ntl). (Entered: 11/16/2021)
11/18/2021	99	NOTICE of Appearance by R. Touhey Myer on behalf of Alkem Laboratories Ltd. (Myer, R.) (Entered: 11/18/2021)
11/22/2021	100	NOTICE OF SERVICE of Alkem Laboratories Ltd.'s Second Supplemental Responses and Objections to Plaintiffs' Common Interrogatory No. 5 filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 11/22/2021)
12/08/2021	101	STIPULATION and [Proposed] Order to Stay Pending Appeal by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 12/08/2021)
12/09/2021		SO ORDERED, re 101 STIPULATION and [Proposed] Order to Stay Pending Appeal (as to certain patents) filed by Azurity Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 12/9/21. (ntl) (Entered: 12/09/2021)
01/06/2022		CORRECTING ENTRY: Notice of Service filed at D.I. 102 has been removed from the docket per request of counsel. (ntl) (Entered: 01/06/2022)
01/12/2022	102	Interim STATUS REPORT by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 01/12/2022)
01/18/2022	103	NOTICE to Take Deposition of Prashant Mandaogade filed by Azurity Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 01/18/2022)
01/18/2022	104	NOTICE to Take Deposition of Somnath Gadhave filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 01/18/2022)
01/18/2022	105	NOTICE to Take Deposition of Ujwal Chhabra filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 01/18/2022)
01/18/2022	106	[SEALED] NOTICE to Take Deposition of Defendant Alkem Laboratories Ltd. Pursuant to Fed. R. Civ. P. 30(b)(6) filed by Azurity Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 01/18/2022)
01/21/2022	107	NOTICE to Take Deposition of Azurity Pharmaceuticals Inc. filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 01/21/2022)
01/21/2022	108	NOTICE to Take Deposition of Michael Beckloff on February 4, 2022 filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 01/21/2022)
01/21/2022	109	NOTICE to Take Deposition of Gerold Mosher on February 8, 2022 filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 01/21/2022)

01/21/2022	110	NOTICE to Take Deposition of David Miles on February 9, 2022 filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 01/21/2022)
01/25/2022	111	REDACTED VERSION of 106 Notice to Take Deposition by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 01/25/2022)
01/28/2022	112	MOTION for Pro Hac Vice Appearance of Attorney Jody Karol - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 01/28/2022)
01/28/2022		SO ORDERED, re (112 in 1:19-cv-02100-LPS, 102 in 1:21-cv-00196-LPS) MOTION for Pro Hac Vice Appearance of Attorney Jody Karol filed by Azurity Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 1/28/22. Associated Cases: 1:19-cv-02100-LPS, 1:21-cv-00196-LPS (ntl) (Entered: 01/28/2022)
01/31/2022	113	NOTICE OF SERVICE of Responses to notice of 30(b)(6) deposition to Alkem filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 01/31/2022)
01/31/2022	114	NOTICE OF SERVICE of Objections and Responses to Defendant's Notice of Rule 30(b)(6) Deposition filed by Azurity Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 01/31/2022)
01/31/2022	115	Supplemental STATUS REPORT by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 01/31/2022)
02/02/2022	116	MOTION for Pro Hac Vice Appearance of Attorney Ty W. Callahan - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 02/02/2022)
02/02/2022		SO ORDERED, re 116 MOTION for Pro Hac Vice Appearance of Attorney Ty W. Callahan filed by Azurity Pharmaceuticals, Inc. Signed by Judge Leonard P. Stark on 2/2/22. (ntl) (Entered: 02/02/2022)
02/03/2022	117	NOTICE to Take Deposition of Manas Pradhan on February 3, 2022 filed by Azurity Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 02/03/2022)
02/10/2022	118	NOTICE OF SERVICE of Amended Infringement Claim Charts filed by Azurity Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 02/10/2022)
02/10/2022	119	NOTICE OF SERVICE of Defendant Alkem Laboratories Ltd.'s First Supplemental Invalidity Contentions regarding U.S. Patent Nos. 10,786,482 B2 and 10,918,621 B2 filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 02/10/2022)
02/22/2022	120	NOTICE OF SERVICE of Defendant Alkem Laboratories Ltd.'s Amended First Supplemental Invalidity Contentions regarding U.S. Patent Nos. 10,786,482 B2 and 10,918,621 B2 filed by Alkem Laboratories Ltd..(Dorsney, Kenneth) (Entered: 02/22/2022)
02/23/2022	121	ORAL ORDER: IT IS HEREBY ORDERED that in anticipation of reassignment of these cases (C.A. Nos. 18-1962, 19-1067, 19-2100, 21-196, 21-1286, 21-1455, 21-1707) to another judge, the parties shall meet and confer and, no later than February 25, submit a joint status report (one that collectively addresses all of these related cases), advising the Court of the following (in addition to anything else the parties wish to report): (i) whether trial has occurred and/or is scheduled to occur and if so, when; (ii) whether a preliminary injunction motion has been litigated and whether any preliminary injunction motion is anticipated; (iii) the date of expiration of any regulatory stay, if applicable; and (iv) the status of any pending motions, or any motions the parties anticipate filing, and the urgency (if any) of such motions. ORDERED by Judge Leonard P. Stark on 2/23/22. Associated Cases: 1:18-cv-01962-LPS et al. (ntl) (Entered: 02/23/2022)

02/25/2022	122	Joint STATUS REPORT by Azurity Pharmaceuticals, Inc., Silvergate Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 02/25/2022)
03/02/2022		Case Reassigned to Judge Mitchell S. Goldberg of the United States District Court for the Eastern District of Pennsylvania. Please include the initials of the Judge (MSG) after the case number on all documents filed. Associated Cases: 1:18-cv-01962-MSG, 1:19-cv-01067-MSG, 1:19-cv-02100-MSG, 1:20-cv-01256-MSG, 1:21-cv-00196-MSG, 1:21-cv-01286-MSG, 1:21-cv-01455-MSG, and 1:21-cv-01707-MSG. (rjb) (Entered: 03/02/2022)
03/03/2022	123	MOTION for Pro Hac Vice Appearance of Attorney Michael P. Hogan - filed by Alkem Laboratories Ltd.. (Dorsney, Kenneth) (Entered: 03/03/2022)
03/07/2022	124	ORDER granting 123 Motion to Appear Pro Hac Vice for Michael P. Hogan. Signed by Judge Mitchell S. Goldberg on 03/07/2022. (smg) (Entered: 03/07/2022)
03/07/2022	125	STIPULATION and [Proposed] Order Amending Case Schedule re 83 SO ORDERED,, Set Deadlines/Hearings, by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 03/07/2022)
03/09/2022	126	NOTICE OF SERVICE of Second Amended Infringement Claim Charts filed by Azurity Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 03/09/2022)
03/18/2022	127	STIPULATION and ORDER Amending Case Schedule. Signed by Judge Mitchell S. Goldberg on 3/18/2022. (nmg) (Entered: 03/18/2022)
03/21/2022	128	STIPULATION and [Proposed] Order Amending Case Schedule by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 03/21/2022)
03/22/2022	129	STIPULATION and ORDER AMENDING CASE SCHEDULE: Opening Expert Reports due by 4/13/2022. Rebuttal Expert Reports due by 5/6/2022. Reply Expert Reports due by 6/1/2022. Expert Discovery due by 6/14/2022. Signed by Judge Mitchell S. Goldberg on 3/21/2022. (nmg) (Entered: 03/22/2022)
03/30/2022	130	ORDER, A status conference will be held on the record, by video conference, on Monday, April 25, 2022, at 3:00 p.m. Chambers will contact the parties with details for joining the video conference. Counsel for all parties shall meet and confer and, within fourteen (14) days of the date of this Order, file a joint letter summarizing the status of each of the above cases. Signed by Judge Mitchell S. Goldberg on 3/30/2022. Associated Cases: 1:18-cv-01962-MSG et al. (nmg) (Entered: 03/30/2022)
04/01/2022	131	[SEALED] Letter to The Honorable Mitchell S. Goldberg from Megan E. Dellinger regarding current schedule. (Dellinger, Megan) (Entered: 04/01/2022)
04/04/2022	132	NOTICE of Withdrawal of Kenneth L. Dorsney, Cortlan S. Hitch and Morris James LLP for Alkem Laboratories Ltd. by Alkem Laboratories Ltd. (Myer, R.) (Entered: 04/04/2022)
04/11/2022		CASE NO LONGER REFERRED to Magistrate Judge Burke for the purpose of exploring ADR. Please see the Court's Standing Order No. 2022-2 dated March 14, 2022. (dlb) (Entered: 04/11/2022)
04/12/2022	133	REDACTED VERSION of 131 Letter by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 04/12/2022)
04/13/2022	134	Joint STATUS REPORT by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 04/13/2022)
04/13/2022	135	NOTICE OF SERVICE of Opening Expert Report of Panayiotis P. Constantinides, Ph.D. filed by Alkem Laboratories Ltd..(Myer, R.) (Entered: 04/13/2022)

04/14/2022	136	NOTICE OF SERVICE of Opening Expert Report of Dr. Steven Little filed by Azurity Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 04/14/2022)
04/25/2022		Minute Entry for proceedings held before Judge Mitchell S. Goldberg - Zoom Status Conference held on 4/25/2022. (Court Reporter Jimmy Cruz.) Associated Cases: 1:18-cv-01962-MSG et al. (nmg) (Entered: 04/26/2022)
05/02/2022	137	Official Transcript of Status Hearing held on 4/25/2022 before Judge Mitchell S. Goldberg. Court Reporter/Transcriber Michael T. Keating, Phone: (609) 440-2177. Transcript may be viewed at the court public terminal or order/purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER Redaction Request due 5/23/2022. Redacted Transcript Deadline set for 6/2/2022. Release of Transcript Restriction set for 8/1/2022. Associated Cases: 1:18-cv-01962-MSG et al.(nmg) (Entered: 05/02/2022)
05/09/2022	138	NOTICE OF SERVICE of (1) Responsive Expert Report of Dr. Steven Little on the Validity of U.S. Patent Nos. 10,786,482 and 10,918,621 and (2) Expert Report of John D. Mahan, J.R., M.D. on Objective Indicia of Non-Obviousness for U.S. Patents 10,786,482 and 10,918,621 filed by Azurity Pharmaceuticals, Inc..(Dellinger, Megan) (Entered: 05/09/2022)
05/09/2022	139	NOTICE OF SERVICE of Noninfringement Rebuttal Expert Report of Barrett E. Rabinow, Ph.D. filed by Alkem Laboratories Ltd..(Myer, R.) (Entered: 05/09/2022)
05/12/2022	140	Letter to The Honorable Christopher J. Burke from Megan E. Dellinger regarding discovery dispute and request to expedite. (Dellinger, Megan) (Entered: 05/12/2022)
05/12/2022	141	ORAL ORDER Setting Teleconference: The Court has reviewed Plaintiff's May 12, 2022 letter requesting an expedited discovery dispute teleconference regarding one discovery dispute. (D.I. 140) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Court's October 12, 2021 Oral Order, (D.I. 87), will be modified as follows with regard to this dispute: (1) The parties shall meet and confer regarding the dispute by close of business on May 13, 2022.; (2) To the extent the parties' dispute is not resolved during the meet and confer process, the parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website. (If the parties dispute is resolved during that process, the parties should file a joint letter advising the Court as such.); (3) Assuming it is needed, a discovery dispute teleconference is set for May 23, 2022 at 2:30 PM before Judge Christopher J. Burke.; (4) By May 16, 2022, Plaintiff shall file with the Court a letter, not to exceed three (3) single-spaced pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By May 19, 2022, Defendant may file a letter, not to exceed three (3) single-spaced pages, in no less than 12-point font, outlining its reasons for its opposition.; (5) The parties should also consult and follow Judge Burke's "Guidelines for Discovery Disputes," which is found in the "Guidelines" tab on Judge Burke's portion of the District Court's website.; (6) By no later than May 19, 2022, the parties shall jointly provide the Court's Courtroom Deputy, Deborah Benyo, with a dial-in number via e-mail to use for the call.; and (7) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 5/12/2022. (dlb) (Entered: 05/12/2022)
05/12/2022		Pro Hac Vice Attorney T.O. Kong for Azurity Pharmaceuticals, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (mpb) (Entered: 05/12/2022)
05/13/2022		Pro Hac Vice Attorney Michael P. Hogan for Alkem Laboratories Ltd. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the

		registered users of CM/ECF and shall be required to file all papers. (apk) (Entered: 05/13/2022)
05/16/2022	142	Joint MOTION for Teleconference to Resolve Discovery Disputes - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 05/16/2022)
05/16/2022	143	[SEALED] Letter to The Honorable Christopher J. Burke from Megan E. Dellinger regarding discovery dispute. (Attachments: # 1 Exhibits A-C, # 2 Text of Proposed Order) (Dellinger, Megan) (Entered: 05/16/2022)
05/19/2022	144	[SEALED] Letter to The Honorable Christopher J. Burke from R Touhey Myer regarding Defendant's Response in Opposition to Plaintiff's Letter Regarding Discovery Dispute - re 141 Order Setting Teleconference,,,,,,,,, (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Text of Proposed Order, # 4 Certificate of Service)(Myer, R.) (Entered: 05/19/2022)
05/19/2022	145	[SEALED] DECLARATION re 144 Letter, <i>Declaration of George J. Barry III in Support of Opposition to Plaintiff's Letter to the Honorable Christopher J. Burke Regarding Discovery Dispute</i> by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 05/19/2022)
05/23/2022		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 5/23/2022. The Court heard argument from the parties' regarding Plaintiff's motion, (D.I. 142). The Court resolved some of the motion during the teleconference. The transcript shall serve as the substance of the Court's order. The Court will issue an order resolving the remaining portion of the motion shortly. (Court Reporter Michele Rolfe. Clerk: M. Crawford) Appearances: M. Dellinger, K. Hanson for Plaintiff; T. Myer, G. Barry for Defendant. (mlc) (Entered: 05/23/2022)
05/23/2022	146	REDACTED VERSION of 143 Letter by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 05/23/2022)
05/24/2022	147	ORAL ORDER: With regard to the remaining portion of Plaintiff's discovery dispute motion, (the "Motion"), (D.I. 142), that the Court did not resolve during the May 23, 2022 teleconference with the parties, the Court hereby ORDERS that Plaintiff's request is DENIED. Here, Plaintiff argues that portions of paragraph 6 as well as paragraphs 81-105 and 137-42 (the "paragraphs at issue") of the Rabinow Report should be stricken because they contain previously undisclosed invalidity opinions relating to patent utility and enablement. (D.I. 143 at 2) However, Defendant's responsive letter attached certain of its prior non-infringement contentions, in which it made clear that Defendant intended to make a non-infringement argument that the scope of certain asserted claims excludes formulations containing both parabens and sugars or sugar alcohols (and that the specification of certain patents warns against the use of paraben preservatives in conjunction with specific sugars and sugar alcohols)and that Defendant is in fact making that same non-infringement argument in the paragraphs at issue. (D.I. 144, ex. A at 3, 5; see also, e.g., D.I. 39, ex. F at 13:9-15) To the extent that Plaintiff responded by asserting that the content of the paragraphs at issue was not sufficiently disclosed in Defendants prior non-infringement contentions because the paragraphs at issue discuss toxicity associated with combining parabens and sugar/sugar alcohols, the Court does not agree. The paragraphs at issue expand upon Defendant's previously-disclosed non-infringement position, and an expert is permitted to expand upon previously-disclosed theories. See, e.g., TQ Delta, LLC v. ADTRAN, Inc., Civil Action No. 14-954-RGA, 2021 WL 3728919, at *4 (D. Del. Aug. 23, 2021). Ordered by Judge Christopher J. Burke on 5/24/2022. (dlb) (Entered: 05/24/2022)
05/26/2022	148	MOTION for Pro Hac Vice Appearance of Attorney Evan T. Sumner - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 05/26/2022)

05/26/2022	149	REDACTED VERSION of 144 Letter, to <i>The Honorable Christopher J. Burke from R Touhey Myer regarding Defendant's Response in Opposition to Plaintiff's Letter Regarding Discovery Dispute</i> by Alkem Laboratories Ltd.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Text of Proposed Order, # 4 Certificate of Service)(Myer, R.) (Entered: 05/26/2022)
05/26/2022	150	REDACTED VERSION of 145 Declaration of <i>George J. Barry III in Support of Opposition to Plaintiff's Letter to the Honorable Christopher J. Burke Regarding Discovery Dispute</i> by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 05/26/2022)
05/31/2022	151	ORDER granting 148 Motion to Appear Pro Hac Vice for Evan T. Sumner. Signed by Judge Mitchell S. Goldberg on 5/31/2022. (twk) (Entered: 05/31/2022)
05/31/2022	152	ORDER, the 5-day Bench Trial scheduled for August 8, 2022 is RESCHEDULED to be held on Tuesday, August 16, 2022 in a Courtroom to be determined in Wilmington, Delaware. Signed by Judge Mitchell S. Goldberg on 5/31/2022. (twk) (Entered: 05/31/2022)
06/01/2022	153	NOTICE OF SERVICE of Defendant's Reply Expert Report of Barrett E. Rabinow, Ph.D. in Support of Patent Invalidity filed by Alkem Laboratories Ltd..(Myer, R.) (Entered: 06/01/2022)
06/01/2022	154	NOTICE OF SERVICE of Defendant's Reply Expert Report of Panayiotis P. Constantinides, Ph.D. in Support of Invalidity filed by Alkem Laboratories Ltd..(Myer, R.) (Entered: 06/01/2022)
06/02/2022	155	NOTICE OF SERVICE of Reply Report of Dr. Steven Little Regarding Infringement of U.S. Patent Nos. 10,786,482 and 10,918,621 filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 06/02/2022)
06/02/2022	156	[SEALED] Letter to The Honorable Christopher J. Burke from Megan E. Dellinger regarding Regarding Rabinow Reply Report. (Attachments: # 1 Exhibits A-D)(Dellinger, Megan) (Entered: 06/02/2022)
06/03/2022	157	[SEALED] Letter to The Honorable Christopher J. Burke from R Touhey Myer regarding Rabinow Reply Report - re 156 Letter. (Attachments: # 1 Exhibit A)(Myer, R.) (Entered: 06/03/2022)
06/07/2022	158	ORAL ORDER: The Court, having reviewed the parties' letters regarding Dr. Rabinow's reply report (the "Rabinow reply report"), (D.I. 156; D.I. 157), hereby ORDERS as follows: (1) Because Plaintiff is requesting that the Court strike material in the Rabinow reply report (whereas the Court's prior order pertained to Dr. Rabinow's responsive report), Plaintiff should have followed the Court's regular discovery dispute procedures to raise this issue.; (2) The Court offers the following guidance as to how it would probably look at the issue based on the limited information it currently has before it: Just because the Court struck certain content with respect to the prior dispute, (D.I. 147), that does not mean that there is no chance that Defendant could utilize the material no matter what. Rather, the relevant questions would be: (a) whether this content truly is responsive to a secondary considerations argument put forward by Plaintiff's expert; and (b) whether this content should have been earlier disclosed in the case by Defendant (such as if, for example, Plaintiff earlier propounded an interrogatory request regarding Defendant's response to Plaintiff's already-disclosed secondary considerations arguments). If the answer to (a) is yes and the answer to (b) is no, then presumably it would be okay for this content to appear in Dr. Rabinow's reply report. But if the answer to (a) is yes and the answer to (b) is yes, then presumably this material would be untimely disclosed, and application of the Pennypack factors would not likely save this material, with trial coming up in August.; (3) The parties should further meet and confer in light of the

		Court's guidance by close of business on June 8, 2022.; (4) To the extent the parties' dispute is not resolved during the meet and confer process, the parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website. (If the parties' dispute is resolved during that process, the parties should file a joint letter advising the Court as such.); (5) Assuming it is needed, a discovery dispute teleconference is set for July 5, 2022 at 1:00 PM before Judge Christopher J. Burke.; (6) By June 14, 2022, Plaintiff shall file with the Court a letter, not to exceed three (3) single-spaced pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By June 21, 2022, Defendant may file a letter, not to exceed three (3) single-spaced pages, in no less than 12-point font, outlining its reasons for its opposition.; (7) The parties should also consult and follow Judge Burke's "Guidelines for Discovery Disputes," which is found in the "Guidelines" tab on Judge Burke's portion of the District Court's website.; (8) By no later than June 29, 2022, the parties shall jointly provide the Court's Courtroom Deputy, Deborah Benyo, with a dial-in number via e-mail to use for the call.; (9) The Court may choose to resolve the Motion prior to the telephone conference and will, in that event, cancel the conference (however, if any party advises the Court in advance that a newer attorney will argue the Motion, see Standing Order Regarding Courtroom Opportunities for Newer Attorneys, https://www.ded.uscourts.gov/sites/ded/files/StandingOrder2017.pdf , then the Court will go forward with the conference).; and (10) To the extent that Dr. Rabinow's deposition must occur in the meantime, (D.I. 156 at 2), Plaintiff shall assume that the material at issue is in the case for now and proceed accordingly at the deposition. Ordered by Judge Christopher J. Burke on 6/7/2022. (dlb) (Entered: 06/07/2022)
06/09/2022	159	NOTICE to Take Deposition of John D. Mahan, Jr., M.D. on June 10, 2022 filed by Alkem Laboratories Ltd..(Myer, R.) (Entered: 06/09/2022)
06/09/2022	160	NOTICE to Take Deposition of Dr. Steven Little on June 14, 2022 filed by Alkem Laboratories Ltd..(Myer, R.) (Entered: 06/09/2022)
06/09/2022	161	REDACTED VERSION of 156 Letter by Azurity Pharmaceuticals, Inc.. (Attachments: # 1 Exhibits A-D)(Dellinger, Megan) (Entered: 06/09/2022)
06/10/2022	162	REDACTED VERSION of 157 Letter to <i>The Honorable Christopher J. Burke from R Touhey Myer regarding Rabinow Reply Report</i> by Alkem Laboratories Ltd.. (Attachments: # 1 Exhibit A)(Myer, R.) (Entered: 06/10/2022)
06/14/2022	163	Joint MOTION for Teleconference to Resolve Discovery Dispute - filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 06/14/2022)
06/14/2022	164	[SEALED] Letter to The Honorable Christopher J. Burke from Megan E. Dellinger regarding discovery dispute. (Attachments: # 1 Exhibits A-L, # 2 Text of Proposed Order) (Dellinger, Megan) (Entered: 06/14/2022)
06/21/2022	165	[SEALED] Letter to The Honorable Christopher J. Burke from R Touhey Myer regarding Defendant's Response in Opposition to Plaintiff's Letter Regarding Discovery Dispute - re 158 Order Setting Teleconference,,,,,,,,,,,,,. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Text of Proposed Order, # 9 Certificate of Service)(Myer, R.) (Entered: 06/21/2022)
06/21/2022	166	[SEALED] DECLARATION re 165 Letter, <i>Declaration of George J. Barry III in Support of Defendant's Response in Opposition to Plaintiff's Letter to the Honorable Christopher J. Burke Regarding Discovery Dispute</i> by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 06/21/2022)

06/21/2022	167	Letter to The Honorable Christopher J. Burke from R Touhey Myer regarding Joint Letter re Motion for Teleconference to Resolve Discovery Dispute. (Myer, R.) (Entered: 06/21/2022)
06/21/2022	168	MOTION for Teleconference to Resolve Discovery Dispute re 167 Letter - filed by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 06/21/2022)
06/23/2022	169	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' June 21, 2022 letter requesting a discovery dispute teleconference regarding one discovery dispute. (D.I. 167) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order will be modified as follows with regard to this dispute: (1) A discovery dispute teleconference is set for July 11, 2022 at 11:00 AM before Judge Christopher J. Burke.; (2) By June 29, 2022, any party seeking relief shall file with the Court a letter, not to exceed three (3) single-spaced pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By July 6, 2022, any party opposing the application for relief may file a letter, not to exceed three (3) single-spaced pages, in no less than 12-point font, outlining that party's reasons for its opposition.; (3) The parties should also consult and follow Judge Burke's "Guidelines for Discovery Disputes," which is found in the "Guidelines" tab on Judge Burke's portion of the District Court's website.; (4) By no later than June 30, 2022, the parties shall jointly provide the Court's Courtroom Deputy, Ms. Benyo, with a dial-in number via e-mail to use for the call.; and (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the teleconference (however, if any party advises the Court in advance that a newer attorney will argue the dispute, see Standing Order Regarding Courtroom Opportunities for Newer Attorneys, https://www.ded.uscourts.gov/sites/ded/files/StandingOrder2017.pdf , then the Court will go forward with the conference). Ordered by Judge Christopher J. Burke on 6/23/2022. (dlb) (Entered: 06/23/2022)
06/28/2022	170	REDACTED VERSION of 165 Letter, <i>to The Honorable Christopher J. Burke from R Touhey Myer regarding Defendant's Response in Opposition to Plaintiff's Letter Regarding Discovery Dispute</i> by Alkem Laboratories Ltd.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Text of Proposed Order, # 9 Certificate of Service)(Myer, R.) (Entered: 06/28/2022)
06/28/2022	171	REDACTED VERSION of 166 Declaration, <i>of George J. Barry III in Support of Defendant's Response in Opposition to Plaintiff's Letter to the Honorable Christopher J. Burke Regarding Discovery Dispute</i> by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 06/28/2022)
06/29/2022	172	[SEALED] Letter to The Honorable Christopher J. Burke from R Touhey Myer regarding Discovery Dispute - re 169 Order Setting Teleconference,,,,,,. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Text of Proposed Order, # 4 Certificate of Service)(Myer, R.) (Entered: 06/29/2022)
06/29/2022	173	[SEALED] DECLARATION re 172 Letter, <i>Declaration of George J. Barry III in Support of Defendant's Letter to the Honorable Christopher J. Burke Regarding Discovery Dispute</i> by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 06/29/2022)
06/30/2022	174	REDACTED VERSION of 164 Letter by Azurity Pharmaceuticals, Inc.. (Attachments: # 1 Exhibits A-L, # 2 Text of Proposed Order)(Dellinger, Megan) (Entered: 06/30/2022)
07/05/2022		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 7/5/2022. The Court heard argument from the parties regarding Plaintiff's discovery dispute motion, (D.I. 163). The Court will issue an order resolving the motion. (Court Reporter Ellie Corbett. Clerk: M. Crawford) Appearances: M.

		Dellinger, W. Devine for Plaintiff; T. Myer, G. Barry, M. Hogan for Defendant. (mlc) (Entered: 07/05/2022)
07/06/2022	175	REDACTED VERSION of 172 Letter, to <i>The Honorable Christopher J. Burke from R Touhey Myer regarding Discovery Dispute</i> by Alkem Laboratories Ltd.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Text of Proposed Order, # 4 Certificate of Service)(Myer, R.) (Entered: 07/06/2022)
07/06/2022	176	REDACTED VERSION of 173 Declaration of <i>George J. Barry III in Support of Defendant's Letter to the Honorable Christopher J. Burke Regarding Discovery Dispute</i> by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 07/06/2022)
07/06/2022	177	[SEALED] Letter to The Honorable Christopher J. Burke from Megan E. Dellinger regarding discovery dispute - re 172 Letter, 169 Order Setting Teleconference,,,,,, (Attachments: # 1 Exhibit A)(Dellinger, Megan) (Entered: 07/06/2022)
07/11/2022	178	ORAL ORDER: The Court, having reviewed Plaintiff's discovery dispute motion ("Plaintiff's motion"), (D.I. 163), and the briefing related thereto, (D.I. 164; D.I. 165), and having heard argument on July 5, 2022, hereby ORDERS that Plaintiff's motion is DENIED for the reasons that follow: (1) Plaintiff's first argument -- and Plaintiff's primary reason for bringing its motion -- is that paragraphs 42-50 (the "paragraphs at issue") of the Rabinow Reply Report should be stricken because their content amounts to a shadow anticipation argument (that is, that Defendant means to use these paragraphs at issue to argue at trial that Allen 1998 and Vasotec anticipate certain of the asserted claims at issue). (D.I. 164 at 1) However, the Court has already ruled during the May 23, 2022 discovery dispute teleconference that Defendant's expert is not permitted to introduce such an argument. And Defendant has represented that they will not be relying on the paragraphs at issue to make a shadow anticipation argument. Rather, Defendant contends that the paragraphs at issue are relevant to objective indicia of nonobviousness. (D.I. 165 at 1, 3) Finally, to the extent that, despite all of this, Defendant does somehow attempt to make an anticipation argument at trial involving Allen 1998 and/or Vasotec, this is a bench trial, and the District Court will simply not permit it.; and (2) Second, Plaintiff argues that the paragraphs at issue are untimely in light of Plaintiff's Interrogatory No. 8 ("ROG No. 8"). (D.I. 164 at 2) The Court will assume arguendo that this is so, even though the history of the objective indicia issue in this case is a little tricky. (Although ROG No. 8 was served long ago, and although Defendant never offered a real substantive response to it, Plaintiff's position as to its own objective indicia case (which would have been helpful for Defendant to understand in responding to ROG No. 8) was not well fleshed out for most of this case.). Nevertheless, even if the paragraphs at issue are considered untimely, after further consideration, the Court concludes that the Pennypack factors weigh against striking them. After all, there are only 9 paragraphs at issue it is not a substantial amount of content. Plus, Plaintiff had the opportunity to question Dr. Rabinow regarding the paragraphs at issue. (See D.I. 164 at 3) And Plaintiff has served a responsive supplemental report (the "supplemental report") from Dr. Little that addresses the paragraphs at issue, (id.), which, as the Court will note below, it will permit Plaintiff to add to the record. Additionally, the Court has also reviewed Defendant's discovery dispute motion ("Defendant's motion"), (D.I. 168), and the briefing related thereto, (D.I. 172; D.I. 177). The Court hereby ORDERS that Defendant's motion also be DENIED. With the motion, Defendant seeks to strike the supplemental report. The Court considers Plaintiff to have previously made a request that the Court permit service of this report, (D.I. 177 at 2-3), which otherwise would be in violation of the operative Scheduling Order, (D.I. 172 at 1-2). The Court concludes that there is good cause to permit such service. Plaintiff was diligent in attempting to serve the supplemental report, having proffered it not long after it became aware of the paragraphs at issue in the Rabinow Reply Report -- and sufficiently in advance of Dr. Little's deposition so that Defendant could question Dr. Little about it. (D.I. 177 at 1-2 & ex. A) Permitting such service will

		not prejudice Defendant (Defendant makes no such argument that it will), and it will allow any possible prejudice to Plaintiff (regarding the Court's decision on Plaintiff's motion) to be mitigated. (D.I. 177 at 1, 3); see also British Telecommc'ns. PLC v. IAC/InterActive Corp, Civil Action No. 18-366-WCB, 2020 WL 3047989, at *2 (D. Del. June 8, 2020). In light of this decision, today's teleconference is CANCELLED. Ordered by Judge Christopher J. Burke on 7/11/2022. (mlc) (Entered: 07/11/2022)
07/11/2022	179	NOTICE OF SERVICE of Supplemental Report of Dr. Steven Little in Response to Dr. Rabinow's Opinions Regarding Allen 1998 filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 07/11/2022)
07/13/2022	180	ORDER, A Telephonic Pretrial Conference is set for 7/29/2022 at 01:00 PM before Judge Mitchell S. Goldberg. (See Order for dial-in information) Signed by Judge Mitchell S. Goldberg on 7/13/2022. (smg) (Entered: 07/13/2022)
07/22/2022	181	REDACTED VERSION of 177 Letter by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 07/22/2022)
07/22/2022	182	[SEALED] Proposed Pretrial Order by Azurity Pharmaceuticals, Inc.. (Attachments: # 1 Exhibits 1-12)(Dellinger, Megan) (Entered: 07/22/2022)
07/29/2022		Minute Entry for proceedings held before Judge Mitchell S. Goldberg - Telephonic Pretrial Conference held on 7/29/2022. (Court Reporter Carl Hauger.) (nmg) (Entered: 07/29/2022)
08/01/2022	183	REDACTED VERSION of 182 Proposed Pretrial Order by Azurity Pharmaceuticals, Inc.. (Attachments: # 1 Exhibits 1-12)(Dellinger, Megan) (Entered: 08/01/2022)
08/03/2022	184	Official Transcript of Pretrial Teleconference held on 7/29/2022 before Judge Mitchell S. Goldberg. Court Reporter/Transcriber: Michael T. Keating. Transcript may be viewed at the court public terminal or order/purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 8/24/2022. Redacted Transcript Deadline set for 9/6/2022. Release of Transcript Restriction set for 11/1/2022. (twk) (Entered: 08/03/2022)
08/14/2022	185	[SEALED] Amended EXHIBIT re 182 Proposed Pretrial Order -- <i>Amended Exhibit 1 to Proposed Pretrial Order</i> -- by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 08/14/2022)
08/16/2022		Minute Entry for proceedings held before Judge Mitchell S. Goldberg - Bench Trial Day 1 held on 8/16/2022. Local Counsel for Plaintiff: Megan Dellinger. Local Counsel for Defendant: R. Touhey Myer. Opening Statements made. Witnesses: Michael Beckloff, Dr. Steven R. Little, Dr. Barret E. Rabinow, Deposition of Ujwal Chhabra, Deposition of Manas Pradhan.(Court Reporter Deanna Warner: warnerdeanna@gmail.com). (srs) (Entered: 08/17/2022)
08/17/2022		Minute Entry for proceedings held before Judge Mitchell S. Goldberg - Bench Trial Day 2 held on 8/17/2022. Local Counsel for Plaintiff: Megan Dellinger. Local Counsel for Defendant: R. Touhey Myer. Witnesses: Deposition of David Miles, Deposition of Gerold Mosher, Dr. Panayiotis P. Constantinides, Dr. John D. Mahan, Jr., Dr. Steven R. Little. (Court Reporter Deanna Warner - warnerdeanna@gmail.com.) (srs) (Entered: 08/17/2022)
08/18/2022		Minute Entry for proceedings held before Judge Mitchell S. Goldberg: Bench Trial Day 3 - Trial Completed on 8/18/2022. Local Counsel for Plaintiff: Megan Dellinger. Local Counsel for Defendant: R. Touhey Myer. Witness: Dr. Steven R. Little. (Court Reporter Deanna Warner - warnerdeanna@gmail.com.) (srs) (Entered: 08/18/2022)

08/19/2022	186	Exhibit List from Trial Held from 8/16/2022 to 8/18/2022 by Alkem Laboratories Ltd., Azurity Pharmaceuticals, Inc.(srs) (Entered: 08/19/2022)
08/19/2022	187	Witness List for Bench Trial 8/16/22-8/18/22. (srs) (Entered: 08/19/2022)
08/23/2022	188	REDACTED VERSION of 185 Exhibit to a Document by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 08/23/2022)
08/29/2022	189	[SEALED] Letter to The Honorable Mitchell S. Goldberg from Megan E. Dellinger regarding narrowed list of defenses. (Attachments: # 1 Exhibit A)(Dellinger, Megan) (Entered: 08/29/2022)
08/30/2022	190	[SEALED] Letter to The Honorable Mitchell S. Goldberg from R Touhey Myer regarding re Plaintiff's Letter of August 29, 2022 - re 189 Letter. (Myer, R.) (Entered: 08/30/2022)
09/02/2022	191	ORDER, upon consideration of letters filed by the parties (ECF Nos. 189 & 190), it is hereby ORDERED that Plaintiff's request to direct Defendant to further narrow its noninfringement position is DENIED. Signed by Judge Mitchell S. Goldberg on 9/2/2022. (srs) (Entered: 09/02/2022)
09/06/2022	192	REDACTED VERSION of 190 Letter to <i>The Honorable Mitchell S. Goldberg from R Touhey Myer regarding re Plaintiff's Letter of August 29, 2022</i> by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 09/06/2022)
09/06/2022	193	REDACTED VERSION of 189 Letter by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 09/06/2022)
09/09/2022	194	Official Transcript of Bench Trial Day 1 held on 08/16/2022 before Judge Goldberg. Court Reporter/Transcriber Deanna Warner, Email: warnerdeanna@gmail.com. Transcript may be viewed at the court public terminal or order/purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER Redaction Request due 9/30/2022. Redacted Transcript Deadline set for 10/11/2022. Release of Transcript Restriction set for 12/8/2022. (smg) (Entered: 09/12/2022)
09/09/2022	195	Official Transcript of Bench Trial Day 2 held on 08/17/2022 before Judge Goldberg. Court Reporter/Transcriber Deanna Warner, Email: warnerdeanna@gmail.com. Transcript may be viewed at the court public terminal or order/purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER Redaction Request due 9/30/2022. Redacted Transcript Deadline set for 10/11/2022. Release of Transcript Restriction set for 12/8/2022. (smg) (Entered: 09/12/2022)
09/09/2022	196	Official Transcript of Bench Trial Day 3 held on 08/18/2022 before Judge Goldberg. Court Reporter/Transcriber Deanna Warner, Email: warnerdeanna@gmail.com. Transcript may be viewed at the court public terminal or order/purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER Redaction Request due 9/30/2022. Redacted Transcript Deadline set for 10/11/2022. Release of Transcript Restriction set for 12/8/2022. (smg) (Entered: 09/12/2022)
09/15/2022	197	[SEALED] POST TRIAL BRIEF by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 09/15/2022)
09/15/2022	198	[SEALED] POST TRIAL BRIEF by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 09/15/2022)
09/16/2022	199	Official Transcript of Discovery Hearing held on 09/14/2022 before Judge Goldberg. Court Reporter/Transcriber TK Transcribers, contact: 609-440-2177. Transcript may be

		viewed at the court public terminal or order/purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER Redaction Request due 10/7/2022. Redacted Transcript Deadline set for 10/17/2022. Release of Transcript Restriction set for 12/15/2022. Associated Cases: 1:18-cv-01962-MSG et al.(smg) (Entered: 09/16/2022)
09/20/2022	200	Letter to The Honorable Mitchell S. Goldberg from Megan E. Dellinger regarding request for closing arguments. (Dellinger, Megan) (Entered: 09/20/2022)
09/20/2022	201	Letter to The Honorable Mitchell S. Goldberg from R Touhey Myer regarding re Plaintiff's Letter of September 20, 2022 - re 200 Letter. (Myer, R.) (Entered: 09/20/2022)
09/22/2022	202	REDACTED VERSION of 197 POST Trial Brief - by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 09/22/2022)
09/22/2022	203	REDACTED VERSION of 198 POST Trial Brief by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 09/22/2022)
09/30/2022	204	ORDER: Within fourteen (14) days of the date of this Order, each party shall file a supplemental brief, not to exceed twenty (20) pages in length, addressing the following issues: (See Order for further details). Signed by Judge Mitchell S. Goldberg on 09/30/2022. (smg) (Entered: 09/30/2022)
10/14/2022	205	[SEALED] POST TRIAL BRIEF (<i>Supplemental</i>) by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 10/14/2022)
10/14/2022	206	[SEALED] POST TRIAL BRIEF (<i>Supplemental</i>) by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 10/14/2022)
10/14/2022	207	[SEALED] DECLARATION re 206 POST Trial Brief (<i>Supplemental</i>) by Alkem Laboratories Ltd.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Certificate of Service)(Myer, R.) (Entered: 10/14/2022)
10/21/2022	208	REDACTED VERSION of 206 POST Trial Brief (<i>Supplemental</i>) by Alkem Laboratories Ltd.. (Myer, R.) (Entered: 10/21/2022)
10/21/2022	209	REDACTED VERSION of 207 Declaration re 206 POST Trial Brief (<i>Supplemental</i>) by Alkem Laboratories Ltd.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Certificate of Service)(Myer, R.) (Entered: 10/21/2022)
10/21/2022	210	REDACTED VERSION of 205 POST Trial Brief by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 10/21/2022)
01/09/2023	211	ORDER, ORAL ARGUMENT in the above-captioned case is scheduled for Thursday, January 19, 2023 at 10:00 a.m. in Courtroom 17A, 601 Market Street, Philadelphia, Pennsylvania. Signed by Judge Mitchell S. Goldberg on 1/9/2023. (twk) (Entered: 01/09/2023)
01/19/2023		Minute Entry for an Oral Argument held before Judge Mitchell S. Goldberg - Oral Argument held on 1/19/2023. (Court Reporter Jimmy Cruz.) (apk) (Entered: 01/19/2023)
01/31/2023	212	Official Transcript of Oral Argument held on 1/19/2023 before Judge Mitchell S. Goldberg. Court Reporter/Transcriber Michael T. Keating. Transcript may be viewed at the court public terminal or order/purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER Redaction Request due 2/21/2023. Redacted Transcript Deadline set for 3/3/2023. Release of Transcript Restriction set for 5/1/2023. (apk) (Entered: 01/31/2023)

02/10/2023	214	ORDER: JUDGMENT in favor of Alkem Laboratories Ltd. against Azurity Pharmaceuticals, Inc. (CASE CLOSED). Signed by Judge Mitchell S. Goldberg on 02/10/2023. (smg) (Entered: 02/10/2023)
02/10/2023	213	MEMORANDUM OPINION. Signed by Judge Mitchell S. Goldberg on 02/10/2023. (smg) (Entered: 02/10/2023)
02/10/2023	215	Final Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s)9,669,008 ;9,808,442 ;10,039,745 ;10,154,987 ;10,772,868 ;10,786,482 ;10,918,621. (Attachments: # 1 Memorandum Opinion, # 2 Final Order)(smg) (Entered: 02/10/2023)
02/14/2023	216	NOTICE OF APPEAL to the Federal Circuit of 213 Memorandum Opinion, 214 Order, Judgment . Appeal filed by Azurity Pharmaceuticals, Inc.. (Dellinger, Megan) (Entered: 02/14/2023)
02/14/2023		APPEAL - Credit Card Payment of \$505.00 received re 216 Notice of Appeal (Federal Circuit) filed by Azurity Pharmaceuticals, Inc.. (Filing fee \$505, receipt number ADEDC-4067326.) (Dellinger, Megan) (Entered: 02/14/2023)
02/14/2023		Notification regarding D.I. 216 Notice of Appeal (Federal Circuit) sent to Reporter Rolfe (mpb) (Entered: 02/14/2023)
02/14/2023		Notice of Appeal and Docket Sheet to US Court of Appeals for the Federal Circuit re 216 Notice of Appeal (Federal Circuit). (mpb) (Entered: 02/15/2023)
02/28/2023	217	NOTICE of Docketing Record on Appeal from USCA for the Federal Circuit re 216 Notice of Appeal (Federal Circuit) filed by Azurity Pharmaceuticals, Inc. USCA Case Number 2023-1540 (mpb) (Entered: 02/28/2023)

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Billable Pages:	23	Cost:	2.30



US010786482B2

(12) **United States Patent**
Mosher et al.

(10) **Patent No.: US 10,786,482 B2**(45) **Date of Patent: *Sep. 29, 2020**(54) **ENALAPRIL FORMULATIONS**(71) Applicant: **Silvergate Pharmaceuticals, Inc.**,
Greenwood Village, CO (US)(72) Inventors: **Gerold L. Mosher**, Kansas City, MO
(US); **David W. Miles**, Kansas City,
MO (US)(73) Assignee: **SILVERGATE**
PHARMACEUTICALS, INC.,
Greenwood Village, CO (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.This patent is subject to a terminal dis-
claimer.(21) Appl. No.: **16/177,159**(22) Filed: **Oct. 31, 2018**(65) **Prior Publication Data**
US 2019/0070147 A1 Mar. 7, 2019**Related U.S. Application Data**(63) Continuation of application No. 16/003,994, filed on
Jun. 8, 2018, now Pat. No. 10,154,987, which is a
continuation of application No. 15/802,341, filed on
Nov. 2, 2017, now Pat. No. 10,039,745, which is a
continuation of application No. 15/613,622, filed on
(Continued)(51) **Int. Cl.**
A61K 31/401 (2006.01)
A61K 9/00 (2006.01)
A61K 47/26 (2006.01)
A61K 47/12 (2006.01)(52) **U.S. Cl.**CPC **A61K 31/401** (2013.01); **A61K 9/0053**
(2013.01); **A61K 9/0095** (2013.01); **A61K**
47/12 (2013.01); **A61K 47/26** (2013.01)(58) **Field of Classification Search**CPC **A61K 31/401**; **A61K 47/12**; **A61K 47/26**;
A61K 9/0053; **A61K 9/0095**
See application file for complete search history.(56) **References Cited**

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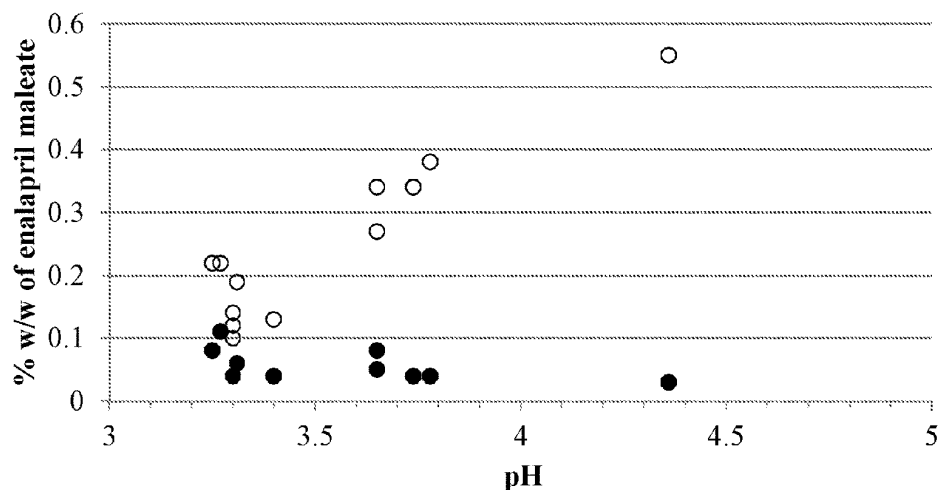
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Primary Examiner — Savitha M Rao(74) *Attorney, Agent, or Firm* — Wilson, Sonsini,
Goodrich & Rosati, P.C.(57) **ABSTRACT**Provided herein are stable enalapril oral liquid formulations.
Also provided herein are methods of using enalapril oral
liquid formulations for the treatment of certain diseases
including hypertension, heart failure and asymptomatic left
ventricular dysfunction.**28 Claims, 2 Drawing Sheets**

● Enalapril diketopiperazine; ○ Enalaprilat

Dist. Delaware
No. 19-2100 (MSG)**PTX-1**

SLVGT_RTU_00003996

US 10,786,482 B2

Page 2

Related U.S. Application Data

Jun. 5, 2017, now Pat. No. 9,808,442, which is a continuation of application No. 15/081,603, filed on Mar. 25, 2016, now Pat. No. 9,669,008.

- (60) Provisional application No. 62/310,198, filed on Mar. 18, 2016.

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Page 4

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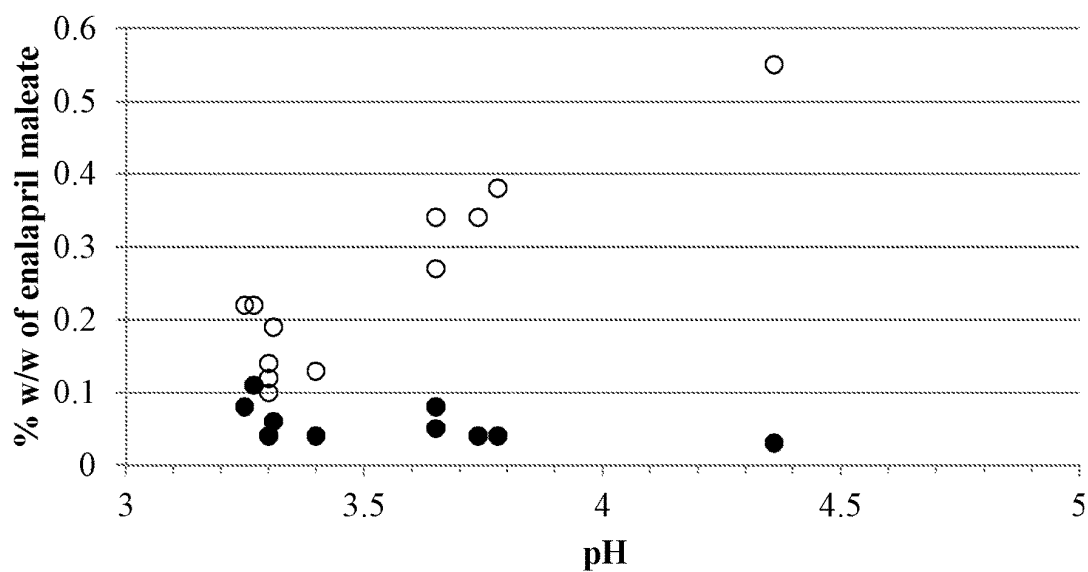
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Sheet 1 of 2

US 10,786,482 B2

FIG. 1

● Enalapril diketopiperazine; ○ Enalaprilat



U.S. Patent

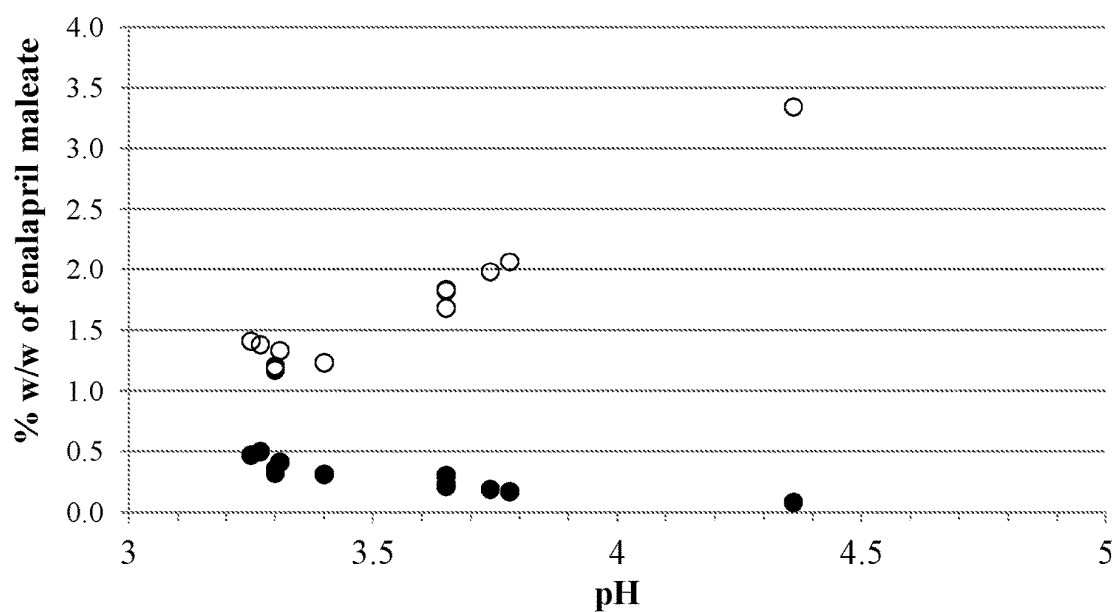
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Sheet 2 of 2

US 10,786,482 B2

FIG. 2

● Enalapril diketopiperazine; ○ Enalaprilat



US 10,786,482 B2

1

ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

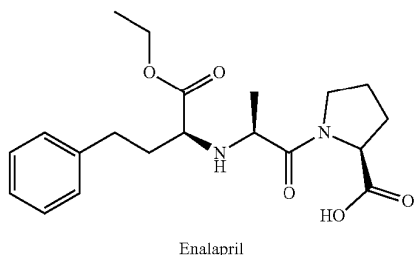
This application is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018, which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

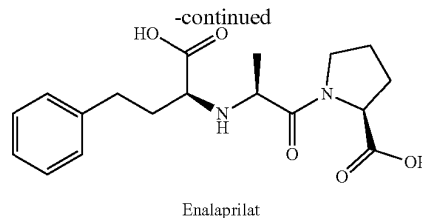
Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralocorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



2



Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5 \pm 3^\circ \text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5 \pm 3^\circ \text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water;

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US 10,786,482 B2

3

wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mmHg. In some embodiments, the subject is an

4

adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed descrip-

US 10,786,482 B2

5

tion that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treat-

6

ment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83

US 10,786,482 B2

7

mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodi-

8

ments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatococin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005-maltodextrin, sorbitol, and fructose combination and Product Code 918.010-water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), Maltisweet™ (maltitol solution, Ingredient), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn

US 10,786,482 B2

9

syrup, Ingredient), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155

10

mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32

US 10,786,482 B2

11

mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5%

12

w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2%

US 10,786,482 B2

13

w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and Preservative Incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

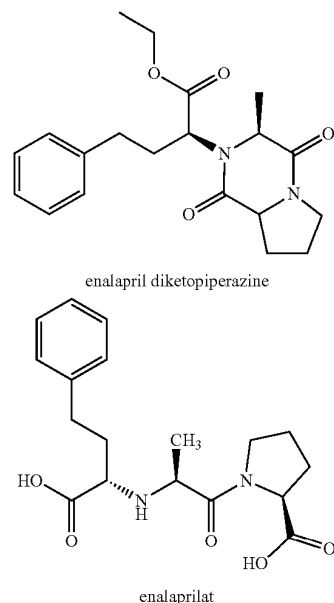
In some embodiments, the oral liquid formulation comprises a buffer.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:

14



In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml,

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US 10,786,482 B2

15

about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/mL, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1 mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/mL, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34%

16

w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1% w/w to about 5% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5% w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/mL, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/mL, about 0.21 mg/mL, about 0.22 mg/mL, about 0.23 mg/mL, about 0.24 mg/mL, about 0.25 mg/mL, about 0.26 mg/mL, about 0.27 mg/mL, about 0.28 mg/mL, about 0.29 mg/mL, about 0.3 mg/mL, about 0.31 mg/mL, about 0.32 mg/mL, about 0.33 mg/mL, about 0.34 mg/mL, about 0.35 mg/mL, about 0.36 mg/mL, about 0.37 mg/mL, about 0.38 mg/mL, about 0.39 mg/mL, about 0.4 mg/mL, about 0.41 mg/mL, about 0.42 mg/mL, about 0.43 mg/mL, about 0.44 mg/mL, about 0.45 mg/mL, about 0.46 mg/mL, about 0.47 mg/mL, about 0.48 mg/mL, about 0.49 mg/mL, about 0.5 mg/mL, about 0.51 mg/mL, about 0.52 mg/mL, about 0.53 mg/mL, about 0.54 mg/mL, about 0.55 mg/mL, about 0.56 mg/mL, about 0.57 mg/mL, about 0.58 mg/mL, about 0.59 mg/mL, about 0.6 mg/mL, about 0.61 mg/mL, about 0.62 mg/mL, about 0.63 mg/mL, about 0.64 mg/mL, about 0.65 mg/mL, about 0.66 mg/mL, about 0.67 mg/mL, about 0.68 mg/mL, about 0.69 mg/mL, about 0.7 mg/mL, about 0.71 mg/mL, about 0.72 mg/mL, about 0.73 mg/mL, about 0.74 mg/mL, about 0.75 mg/mL, about 0.76 mg/mL, about 0.77 mg/mL, about 0.78 mg/mL, about 0.79 mg/mL, or about 0.8 mg/mL in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the

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US 10,786,482 B2

17

oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1% w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise,

18

cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18

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US 10,786,482 B2

19

months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is $5\pm 3^{\circ}\text{C}$. In some embodiments, refrigerated condition is about 2°C ., about 2.1°C ., about 2.2°C ., about 2.3°C ., about 2.4°C ., about 2.5°C ., about 2.6°C ., about 2.7°C ., about 2.8°C ., about 2.9°C ., about 3°C ., about 3.1°C ., about 3.2°C ., about 3.3°C ., about 3.4°C ., about 3.5°C ., about 3.6°C ., about 3.7°C ., about 3.8°C ., about 3.9°C ., about 4°C ., about 4.1°C ., about 4.2°C ., about 4.3°C ., about 4.4°C ., about 4.5°C ., about 4.6°C ., about 4.7°C ., about 4.8°C ., about 4.9°C ., about 5°C ., about 5.1°C ., about 5.2°C ., about 5.3°C ., about 5.4°C ., about 5.5°C ., about 5.6°C ., about 5.7°C ., about 5.8°C ., about 5.9°C ., about 6°C ., about 6.1°C ., about 6.2°C ., about 6.3°C ., about 6.4°C ., about 6.5°C ., about 6.6°C ., about 6.7°C ., about 6.8°C ., about 6.9°C ., about 7°C ., about 7.1°C ., about 7.2°C ., about 7.3°C ., about 7.4°C ., about 7.5°C ., about 7.6°C ., about 7.7°C ., about 7.8°C ., about 7.9°C ., or about 8°C . At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. $25\pm 5^{\circ}\text{C}$.; $55\pm 10\%$ RH). In some instances, an accelerated condition is at about 25°C ., about 30°C ., about 35°C ., about 40°C ., about 45°C ., about 50°C ., about 55°C or about 60°C . In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40°C or 60°C at ambient humidity. In yet further instances, an accelerated condition is about 40°C at $75\pm 5\%$ RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about

20

15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and

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US 10,786,482 B2

21

the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other

embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation. Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and

22

mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof, and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the

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US 10,786,482 B2

23

liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2x10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

24

Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset

US 10,786,482 B2

25

of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of

26

about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76 mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet

US 10,786,482 B2

27

formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to

28

a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxyben-

US 10,786,482 B2

29

zamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltiazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartan, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

“Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

“Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms

30

“patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or

US 10,786,482 B2

31

undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at 60° C.	Formulation					
	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

32

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29

TABLE B-1-continued

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

US 10,786,482 B2

33

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours	Formulation		
at 60° C.	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		

34

TABLE C-1-continued

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)									
25		Storage		Formulation					
		° C.	Weeks	C1	C2	C3	C4	C5	
Liquid Formulations									
30	Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02	
			4	0.02	0.03	0.03	0.03	0.02	
		19-23	8	0.03	0.04	0.04			
			0	0.03	0.04	0.04	0.02	0.02	
	4		0.05	0.09	0.11	0.05	0.04		
	8		0.08	0.17	0.19				
	Enalaprilat	40	0	0.03	0.04	0.04	0.02	0.02	
			4	0.35	0.91	1.10	0.31	0.21	
40		Enalaprilat	5	8	0.65	1.80	2.05		
				0	0.18	0.14	0.12	0.13	0.19
	19-23		4	0.18	0.15	0.12	0.43	0.53	
			8	0.55	0.38	0.34			
			40	0	0.18	0.14	0.12	0.13	0.19
				4	1.35	0.83	0.80	1.75	2.29
			8	3.34	2.06	1.98			
				0	0.18	0.14	0.12	0.13	0.19
	4	10.49	6.08	6.11	12.30	16.14			
		8	24.37	14.12	14.22				

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

US 10,786,482 B2

35

36

TABLE D-1

Composition of Enalapril Maleate Formulations						
Component	D1	D2	D3	D4	D5	D6
Powder Formulation (grams)						
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	° C.	Weeks	D1	D2	D3	D4	D5	D6
Liquid Formulations								
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
		19-23	0	0.04	0.02	0.03	0.03	0.04
	19-23	4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
		40	0	0.04	0.02	0.03	0.03	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
	40	8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
		19-23	0	0.03	0.02	0.03	0.13	0.14
	19-23	4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		

US 10,786,482 B2

37

TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Storage		Formulation					
° C.	Weeks	D1	D2	D3	D4	D5	D6
40	0	0.03	0.02	0.03	0.03	0.13	0.14
	4	4.76	4.42	4.76	6.45	5.55	5.24
	8	8.95	8.64	9.61	12.94	12.73	12.18
	12	11.01	10.64	11.41	16.16		
	26	17.18	17.11	18.30	27.36		

38

Example E: Stability of Solution Formulations of
Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		

-continued

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate	0.75	0.75	0.75	0.75	0.38	0.19
anhydrous						
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)							
Storage		Formulation					
° C.	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03
		8	0.04	0.04	0.04	0.04	0.03
		12	0.05	0.05	0.04	0.05	0.04
		26	0.07	0.06	0.05	0.06	0.05
	19-23	52				0.15	0.14
		62	0.18	0.18	0.16	0.14	
		0	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16
		8	0.35	0.35	0.32	0.31	0.29
		12	0.58	0.59	0.53	0.51	0.48
		26	1.10	1.10	1.00	0.95	0.97
		52				2.30	2.15
	40	62	3.02	3.04	2.75	2.64	
		0	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76
		8	4.02	3.99	3.99	3.62	3.37
		12	6.72	6.42	6.47	6.00	5.53
Enalaprilat	5	5.29					
		0	0.00	0.00	0.01	0.02	0.00
		4	0.07	0.09	0.10	0.11	0.07
		8	0.12	0.14	0.10	0.13	0.09
		12	0.16	0.15	0.15	0.17	0.14
	19-23	26	0.31	0.30	0.29	0.31	0.27
		52				0.54	0.46
		62	0.75	0.75	0.74	0.71	
		0	0.00	0.00	0.01	0.02	0.00
		4	0.65	0.65	0.68	0.70	0.50
		8	1.17	1.19	1.20	1.23	1.03
		12	1.67	1.69	1.72	1.80	1.30
		26	3.36	3.38	3.42	3.57	3.07
		52				6.32	5.88
		62	7.99	8.02	8.04	8.57	

SLVGT_RTU_00004020

US 10,786,482 B2

39

TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Storage		Formulation					
° C.	Weeks	E1	E2	E3	E4	E5	E6
40	0	0.00	0.00	0.01	0.02	0.00	0.00
	4	4.85	4.93	5.19	5.42	3.33	3.25
	8	8.08	8.06	8.56	9.01	6.65	6.35
	12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. 1 (5° C. \pm 3° C.) and FIG. 2 (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution Vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5),

40

to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_m were approximately 115% and

US 10,786,482 B2

41

109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. An oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/mL enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
 - (iii) about 1 mg/mL sodium benzoate; and
 - (iv) water;
 wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5\pm 3^\circ\text{C}$.
2. The oral liquid formulation of claim 1 further comprising a sweetener.
3. The oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. The oral liquid formulation of claim 1 further comprising a flavoring agent.
5. The oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
6. The oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
7. The oral liquid formulation of claim 1, wherein the buffer comprises about 0.8 to about 3.5 mg/mL citric acid.
8. The oral liquid formulation of claim 1, wherein the buffer comprises about 0.1 to about 0.8 mg/mL sodium citrate.
9. The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is less than about 3.5.
10. The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.
11. The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is about 3.3.
12. The oral liquid formulation of claim 1, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about $5\pm 3^\circ\text{C}$.
13. An oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/mL enalapril or a pharmaceutically acceptable salt or solvate thereof;

42

- (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;

- (iii) about 1 mg/mL sodium benzoate;

- (iv) water; and

- (v) optionally a sweetener, a flavoring agent, or both;
- wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about
- $5\pm 3^\circ\text{C}$
- .

14. An oral liquid formulation, comprising:

- (i) about 0.6 to about 1.2 mg/mL enalapril or a pharmaceutically acceptable salt or solvate thereof;

- (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;

- (iii) about 1 mg/mL of a preservative, wherein the preservative is a paraben or a mixture of parabens; and

- (iv) water;

- wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5\pm 3^\circ\text{C}$.

15. The oral liquid formulation of claim 14 further comprising a sweetener.

16. The oral liquid formulation of claim 15, wherein the sweetener is sucralose.

17. The oral liquid formulation of claim 14 further comprising a flavoring agent.

18. The oral liquid formulation of claim 14, wherein the formulation does not contain mannitol.

19. The oral liquid formulation of claim 14, wherein the formulation does not contain silicon dioxide.

20. The oral liquid formulation of claim 14, wherein the pH of the oral liquid formulation is less than about 3.5.

21. The oral liquid formulation of claim 14, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.

22. The oral liquid formulation of claim 14, wherein the pH of the oral liquid formulation is about 3.3.

23. The oral liquid formulation of claim 14, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about $5\pm 3^\circ\text{C}$.

24. The oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/mL.

25. The oral liquid formulation of claim 1, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

26. The oral liquid formulation of claim 1, wherein the buffer is present at a concentration of about 10 mM in the oral liquid formulation.

27. The oral liquid formulation of claim 14, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/mL.

28. The oral liquid formulation of claim 14, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

* * * * *



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(12) **United States Patent**
Mosher et al.

(10) **Patent No.: US 10,918,621 B2**(45) **Date of Patent: *Feb. 16, 2021**(54) **ENALAPRIL FORMULATIONS**(71) Applicant: **Silvergate Pharmaceuticals, Inc.**,
Greenwood Village, CO (US)(72) Inventors: **Gerold L. Mosher**, Kansas City, MO
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PHARMACEUTICALS, INC.,
Greenwood Village, CO (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.This patent is subject to a terminal dis-
claimer.(21) Appl. No.: **16/991,575**(22) Filed: **Aug. 12, 2020**(65) **Prior Publication Data**

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A61K 47/26 (2006.01)
A61K 47/12 (2006.01)(52) **U.S. Cl.**CPC **A61K 31/401** (2013.01); **A61K 9/0053**
(2013.01); **A61K 9/0095** (2013.01); **A61K**
47/12 (2013.01); **A61K 47/26** (2013.01)(58) **Field of Classification Search**CPC **A61K 31/401**; **A61K 47/12**; **A61K 47/26**;
A61K 9/0053; **A61K 9/0095**
See application file for complete search history.(56) **References Cited**

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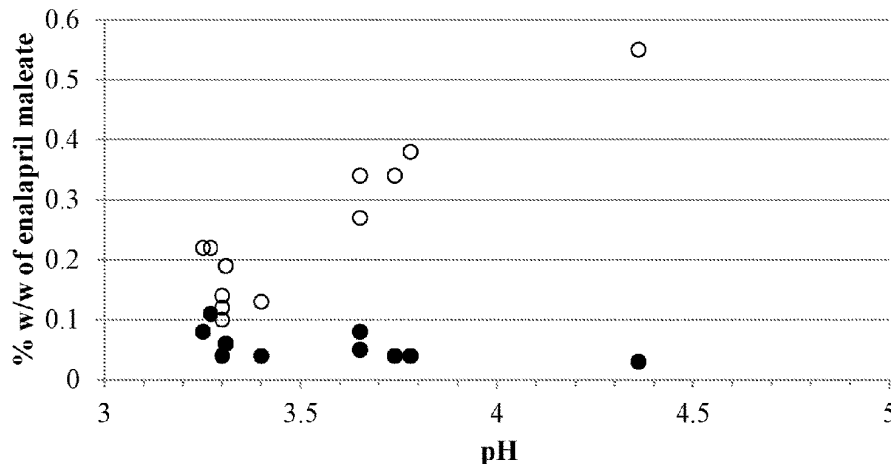
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Primary Examiner — Savitha M Rao(74) *Attorney, Agent, or Firm* Wilson Sonsini Goodrich
& Rosati, P C.(57) **ABSTRACT**Provided herein are stable enalapril oral liquid formulations.
Also provided herein are methods of using enalapril oral
liquid formulations for the treatment of certain diseases
including hypertension, heart failure and asymptomatic left
ventricular dysfunction.**30 Claims, 2 Drawing Sheets**

● Enalapril diketopiperazine; ○ Enalaprilat

Dist. Delaware
No. 19-2100 (MSG)**PTX-2**

SLVGT_RTU_00005394

US 10,918,621 B2

Page 2

Related U.S. Application Data

Jun. 8, 2018, now Pat. No. 10,154,987, which is a continuation of application No. 15/802,341, filed on Nov. 2, 2017, now Pat. No. 10,039,745, which is a continuation of application No. 15/613,622, filed on Jun. 5, 2017, now Pat. No. 9,808,442, which is a continuation of application No. 15/081,603, filed on Mar. 25, 2016, now Pat. No. 9,669,008.

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Page 4

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U.S. Patent

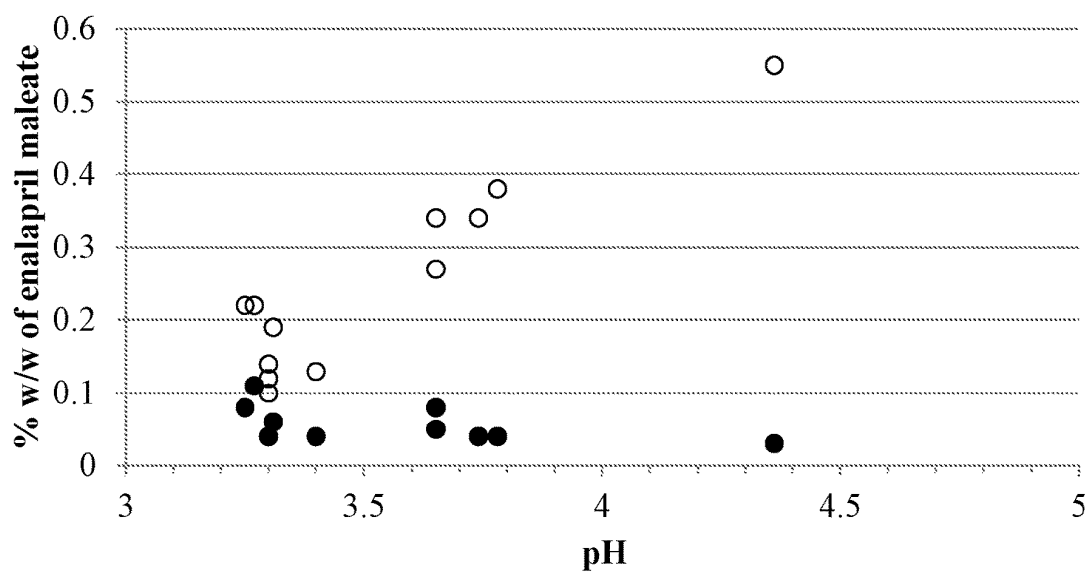
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Sheet 1 of 2

US 10,918,621 B2

FIG. 1

● Enalapril diketopiperazine; ○ Enalaprilat



U.S. Patent

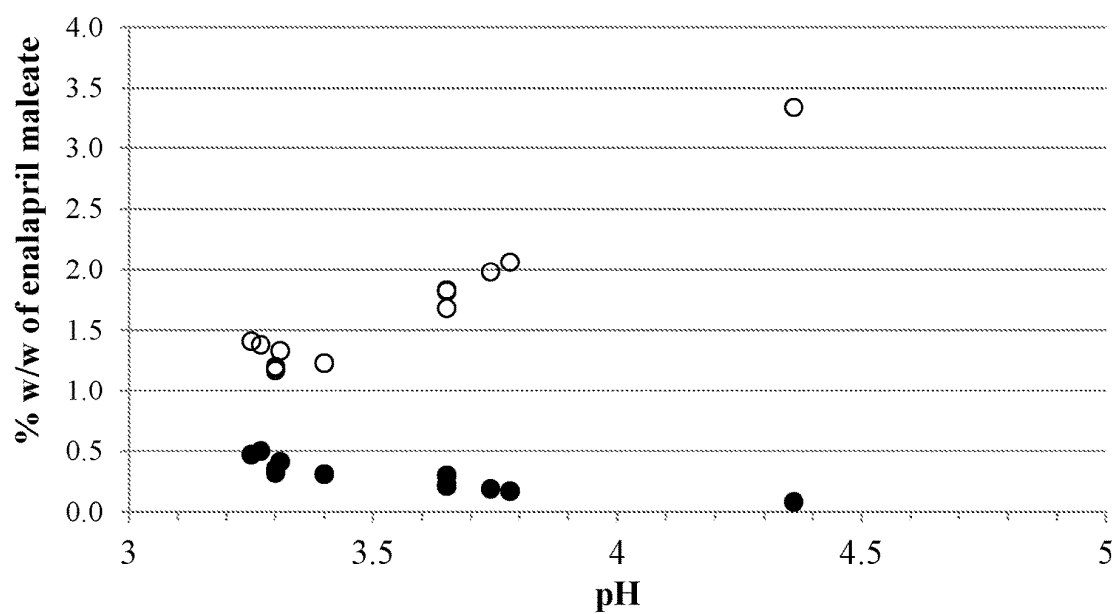
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Sheet 2 of 2

US 10,918,621 B2

FIG. 2

● Enalapril diketopiperazine; ○ Enalaprilat



US 10,918,621 B2

1

ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

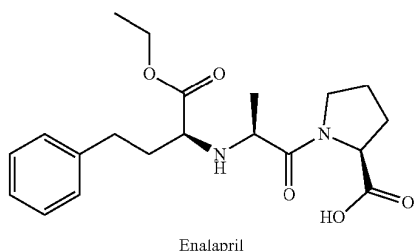
This application is a continuation of U.S. patent application Ser. No. 16/883,553, filed May 26, 2020 which is a continuation of U.S. patent application Ser. No. 16/242,898, filed Jan. 8, 2019, which is a continuation of Ser. No. 16/177,159, filed Oct. 31, 2018, which is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018 (now U.S. Pat. No. 10,154,987, issued Dec. 18, 2018), which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

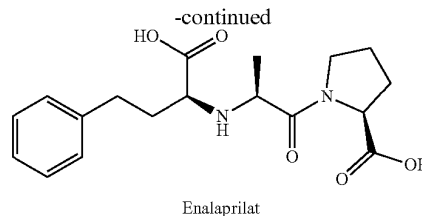
Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralocorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



2



Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5 \pm 3^\circ$ C. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5 \pm 3^\circ$ C. for at least 18 months. In some embodiments, the formulation is stable at about $5 \pm 3^\circ$ C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the

US 10,918,621 B2

3

formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ$ C. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ$ C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ$ C. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ$ C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some

4

embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed descrip-

US 10,918,621 B2

5

tion that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treat-

6

ment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77

US 10,918,621 B2

7

mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable

8

salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatococcus, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003—propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005—maltodextrin, sorbitol, and fructose combination and Product Code 918.010—water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor

US 10,918,621 B2

9

combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), Maltisweet™ (maltitol solution, Ingredion), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

10

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about

US 10,918,621 B2

11

3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w,

12

about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w,

US 10,918,621 B2

13

about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and preservative incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

In some embodiments, the oral liquid formulation comprises a buffer.

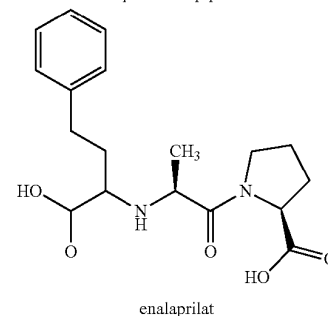
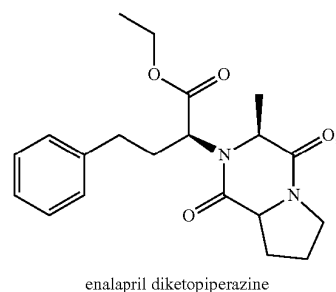
In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises

14

citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodi-

US 10,918,621 B2

15

ments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/ml, about 1.31 mg/ml, about 1.32 mg/ml, about 1.33 mg/ml, about 1.34 mg/ml, about 1.35 mg/ml, about 1.36 mg/ml, about 1.37 mg/ml, about 1.38 mg/ml, about 1.39 mg/ml, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/ml, about 1.61 mg/ml, about 1.62 mg/ml, about 1.63 mg/ml, about 1.64 mg/ml, about 1.65 mg/ml, about 1.66 mg/ml, about 1.67 mg/ml, about 1.68 mg/ml, about 1.69 mg/ml, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/ml, about 1.91 mg/ml, about 1.92 mg/ml, about 1.93 mg/ml, about 1.94 mg/ml, about 1.95 mg/ml, about 1.96 mg/ml, about 1.97 mg/ml, about 1.98 mg/ml, about 1.99 mg/ml, or about 2 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/ml, about 2.05 mg/ml, about 2.1 mg/ml, about 2.15 mg/ml, about 2.2 mg/ml, about 2.25 mg/ml, about 2.3 mg/ml, about 2.35 mg/ml, about 2.4 mg/ml, about 2.45 mg/ml, about 2.5 mg/ml, about 2.55 mg/ml, about 2.6 mg/ml, about 2.65 mg/ml, about 2.7 mg/ml, about 2.75 mg/ml, about 2.8 mg/ml, about 2.85 mg/ml, about 2.9 mg/ml, about 2.95 mg/ml, about 3 mg/ml, about 3.05 mg/ml, about 3.1

16

mg/ml, about 3.15 mg/ml, about 3.2 mg/ml, about 3.25 mg/ml, about 3.3 mg/ml, about 3.35 mg/ml, about 3.4 mg/ml, about 3.45 mg/ml, or about 3.5 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34% w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1% w/w to about 5% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5% w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/ml, about 0.11 mg/ml, about 0.12 mg/ml, about 0.13 mg/ml, about 0.14 mg/ml, about 0.15 mg/ml, about 0.16 mg/ml, about 0.17 mg/ml, about 0.18 mg/ml, about 0.19 mg/ml, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml,

US 10,918,621 B2

17

about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1% w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural

18

or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubble-gum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w,

US 10,918,621 B2

19

about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is $5\pm 3^{\circ}\text{C}$. In some embodiments, refrigerated condition is about 2°C ., about 2.1°C ., about 2.2°C ., about 2.3°C ., about 2.4°C ., about 2.5°C ., about 2.6°C ., about 2.7°C ., about 2.8°C ., about 2.9°C ., about 3°C ., about 3.1°C ., about 3.2°C ., about 3.3°C ., about 3.4°C ., about 3.5°C ., about 3.6°C ., about 3.7°C ., about 3.8°C ., about 3.9°C ., about 4°C ., about 4.1°C ., about 4.2°C ., about 4.3°C ., about 4.4°C ., about 4.5°C ., about 4.6°C ., about 4.7°C ., about 4.8°C ., about 4.9°C ., about 5°C ., about 5.1°C ., about 5.2°C ., about 5.3°C ., about 5.4°C ., about 5.5°C ., about 5.6°C ., about 5.7°C ., about 5.8°C ., about 5.9°C ., about 6°C ., about 6.1°C ., about 6.2°C ., about 6.3°C ., about 6.4°C ., about 6.5°C ., about 6.6°C ., about 6.7°C ., about 6.8°C ., about 6.9°C ., about 7°C ., about 7.1°C ., about 7.2°C ., about 7.3°C ., about 7.4°C ., about 7.5°C ., about 7.6°C ., about 7.7°C ., about 7.8°C ., about 7.9°C ., or about 8°C . At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. $25\pm 5^{\circ}\text{C}$.; $55\pm 10\%$ RH). In some instances, an accelerated condition is at about 25°C ., about 30°C ., about 35°C ., about 40°C ., about 45°C ., about 50°C ., about 55°C ., or about 60°C . In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40°C ., or 60°C ., at ambient humidity. In yet further instances, an accelerated condition is about 40°C ., at $75\pm 5\%$ RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

20

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in

US 10,918,621 B2

21

some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

22

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some

SLVGT_RTU_00005410

US 10,918,621 B2

23

embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2x10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

24

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. $25\pm4^\circ\text{C}$; $55\pm10\%$ RH). In some instances, an accelerated condition is at about 30°C ., about 35°C ., about 40°C ., about 45°C ., about 50°C ., about 55°C . or about 60°C . In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40°C . or 60°C . at ambient humidity. In yet further instances, an accelerated condition is about 40°C . at $75\pm5\%$ RH humidity.

Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and

US 10,918,621 B2

25

secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic

26

and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76 mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

US 10,918,621 B2

27

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility

28

of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

US 10,918,621 B2

29

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxymethamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltiazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lisartan, eprosartan, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a defini-

30

tion that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

“Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

“Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms “patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological

US 10,918,621 B2

31

or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition

32

a condition. As used herein, “treat,” “treated,” “treatment,” or “treating” includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)							
Hours at 60° C.	Formulation						
	A1	A2	A3	A4	A5	A6	
Enalapril Diketopiperazine							
0	0.04	0.03	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53	
180	6.21	1.77	0.75	1.73	1.43	1.07	
Enalaprilat							
0	0.09	0.15	0.29	0.14	0.16	0.12	
97	5.20	16.9	47.4	16.1	20.3	15.6	
180	9.94	34.8	113	33.5	42.2	31.7	

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were

SLVGT_RTU_00005415

US 10,918,621 B2

33

transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours at 60° C.	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula®

34

mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Component	Powder Formulation (grams)				
	C1	C2	C3	C4	C5
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	° C.	Weeks	Liquid Formulations				
			C1	C2	C3	C4	C5
Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
		4	0.02	0.03	0.03	0.03	0.02
		8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.04	0.02	0.02
		4	0.05	0.09	0.11	0.05	0.04
		8	0.08	0.17	0.19		

US 10,918,621 B2

35

TABLE C-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	° C.	Weeks	C1	C2	C3	C4	C5
Liquid Formulations							
Enalaprilat	40	0	0.03	0.04	0.04	0.02	0.02
		4	0.35	0.91	1.10	0.31	0.21
		8	0.65	1.80	2.05		
	5	0	0.18	0.14	0.12	0.13	0.19
		4	0.18	0.15	0.12	0.43	0.53
		8	0.55	0.38	0.34		
	19-23	0	0.18	0.14	0.12	0.13	0.19
		4	1.35	0.83	0.80	1.75	2.29
		8	3.34	2.06	1.98		
	40	0	0.18	0.14	0.12	0.13	0.19
		4	10.49	6.08	6.11	12.30	16.14
		8	24.37	14.12	14.22		

36

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each pow-

dered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations						
Component	D1	D2	D3	D4	D5	D6
Powder Formulation (grams)						
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

SLVGT_RTU_00005417

US 10,918,621 B2

37

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)								
Storage			Formulation					
° C.	Weeks		D1	D2	D3	D4	D5	D6
Liquid Formulations								
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		26	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		
	40	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	4.76	4.42	4.76	6.45	5.55	5.24
		8	8.95	8.64	9.61	12.94	12.73	12.18
		12	11.01	10.64	11.41	16.16		
		26	17.18	17.11	18.30	27.36		

38

Example E: Stability of Solution Formulations of Enalapril Maleate

35

-continued

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C. \pm 3° C., at room temperature (19-23° C.) and at 40° C. \pm 2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
40 Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate	0.75	0.75	0.75	0.75	0.38	0.19
anhydrous						
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
45 Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)								
Storage			Formulation					
° C.	Weeks		E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
	19-23	62	0.18	0.18	0.16	0.14		
		0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28

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US 10,918,621 B2

39

TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)								
Storage		Formulation						
° C.	Weeks	E1	E2	E3	E4	E5	E6	
Enalaprilat	12	0.58	0.59	0.53	0.51	0.48	0.45	
	26	1.10	1.10	1.00	0.95	0.97	0.92	
	52					2.30	2.15	
	62	3.02	3.04	2.75	2.64			
	0	0.01	0.01	0.01	0.01	0.01	0.01	
	4	2.65	2.71	2.60	2.42	1.76	1.68	
	8	4.02	3.99	3.99	3.62	3.37	3.13	
	12	6.72	6.42	6.47	6.00	5.53	5.29	
	0	0.00	0.00	0.01	0.02	0.00	0.00	
	4	0.07	0.09	0.10	0.11	0.07	0.08	
	8	0.12	0.14	0.10	0.13	0.09	0.08	
	12	0.16	0.15	0.15	0.17	0.14	0.11	
	26	0.31	0.30	0.29	0.31	0.27	0.24	
	52					0.54	0.46	
	62	0.75	0.75	0.74	0.71			
	0	0.00	0.00	0.01	0.02	0.00	0.00	
	4	0.65	0.65	0.68	0.70	0.50	0.46	
	8	1.17	1.19	1.20	1.23	1.03	0.95	
	12	1.67	1.69	1.72	1.80	1.30	1.21	
	26	3.36	3.38	3.42	3.57	3.07	2.90	
	52					6.32	5.88	
	62	7.99	8.02	8.04	8.57			
	0	0.00	0.00	0.01	0.02	0.00	0.00	
	4	4.85	4.93	5.19	5.42	3.33	3.25	
	8	8.08	8.06	8.56	9.01	6.65	6.35	
	12	10.70	10.48	11.01	11.97	8.14	7.96	

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. 1 (5° C. \pm 3° C.) and FIG. 2 (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165

30

TABLE G-1-continued

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

45

Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered

US 10,918,621 B2

41

via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirman’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_{max} were approximately 115% and 109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

42

What is claimed is:

1. A stable oral liquid formulation, consisting essentially of:

- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
- (iii) a preservative, wherein the preservative is a paraben or a mixture of parabens; and
- (iv) water;

wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;

wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

2. The stable oral liquid formulation of claim 1, comprising a sweetener.

3. The stable oral liquid formulation of claim 1, comprising a flavoring agent.

4. The stable oral liquid formulation of claim 1, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.

5. The stable oral liquid formulation of claim 1, wherein the buffer concentration is about 10 mM to about 20 mM.

6. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH between about 3 and about 4.

7. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH at about 3.3.

8. The stable oral liquid formulation of claim 1, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.

9. The stable oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.

10. The stable oral liquid formulation of claim 1, wherein the preservative is a mixture of parabens.

11. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is methylparaben, ethylparaben, propylparaben, butylparaben, salts thereof, or a combination thereof.

12. The stable oral liquid formulation of claim 1, wherein the preservative is a mixture of methylparaben and propylparaben.

13. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.

14. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation.

15. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

16. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 2% w/w to about 30% w/w of the solids in the oral liquid formulation.

17. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 18 months.

18. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 24 months.

US 10,918,621 B2

43

19. A stable oral liquid formulation, consisting essentially of:

- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
- (iii) a preservative, wherein the preservative is methylparaben, ethylparaben, propylparaben, butylparaben, or a combination thereof; and

(iv) water;

wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;

wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

20. The stable oral liquid formulation of claim 19, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.

21. The stable oral liquid formulation of claim 19, wherein the buffer concentration is about 10 mM to about 20 mM.

22. The stable oral liquid formulation of claim 19, wherein the buffer maintains the pH between about 3 and about 4.

23. The stable oral liquid formulation of claim 19, wherein the buffer maintains the pH at about 3.3.

24. The stable oral liquid formulation of claim 19, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.

44

25. The stable oral liquid formulation of claim 19, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.

26. The stable oral liquid formulation of claim 19, wherein the preservative is a mixture of parabens that are selected from methylparaben, ethylparaben, propylparaben, and butylparaben.

27. The stable oral liquid formulation of claim 19, wherein the preservative is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.

28. The stable oral liquid formulation of claim 19, wherein the preservative is present at about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation.

29. The stable oral liquid formulation of claim 19, wherein the preservative is present at about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

30. A stable oral liquid formulation, consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer to maintain the pH about 4.5 or below;

(iii) a preservative, wherein the preservative is methylparaben, ethylparaben, propylparaben, butylparaben, or a combination thereof; and

(iv) water;

wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;

wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

* * * * *

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SILVERGATE PHARMACEUTICALS, INC.,)	
)	
Plaintiff,)	
)	
v.)	C.A. No. 19-2100 (LPS)
)	
ALKEM LABORATORIES LTD.,)	
)	
Defendant.)	

FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Silvergate Pharmaceuticals, Inc. (“Silvergate”), by and through its attorneys, brings this First Amended Complaint against Defendant Alkem Laboratories Ltd. (“Alkem”), and alleges as follows:

THE NATURE OF THE ACTION

1. This is an action for patent infringement of United States Patent Nos. 9,669,008 (“’008 patent”), 9,808,442 (“’442 patent”), 10,039,745 (“’745 patent”), 10,154,987 (“’987 patent”), 10,772,868 (“’868 patent”), 10,786,482 (“’482 patent”), and 10,918,621 (the “’621 patent”) (collectively, the “Patents-in-Suit”) under the patent laws of the United States of America, Title 35, United States Code, arising out of the submission by Alkem of Abbreviated New Drug Application (“ANDA”) No. 213714 to the United States Food and Drug Administration (“FDA”) seeking approval of a generic version of Silvergate’s oral solution formulation that is the subject of New Drug Application (“NDA”) No. 208686, hereinafter referred to as Silvergate’s “Epaned[®] Product” or “Epaned[®].” Silvergate seeks all available relief under the patent laws of the United States, 35 U.S.C. § 100 *et seq.*, and other applicable laws for Alkem’s infringement of the Patents-in-Suit.

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April 13, 2021

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC.,

Plaintiff,

v.

ALKEM LABORATORIES LTD.

Defendant.

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C.A. No. 19-2100 (LPS)

FILED UNDER SEAL

**CONTAINS MATERIAL
DESIGNATED AS
CONFIDENTIAL UNDER THE
PROTECTIVE ORDER**

**JOINT CLAIM CONSTRUCTION BRIEF
FOR U.S. PATENT NOS. 10,772,868; 10,786,482; AND 10,918,621**

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August 9, 2021

Alkem demonstrated that the patentee made a clear and unmistakable disavowal of claim scope while prosecuting the patents-in-suit and their parent patent. Azurity argues that the patentee's emphasis during prosecution on the fewer required ingredients in claim 20 of the '008 patent, and the claim's use of "consists essentially of" should be given less weight because the section that it is a part of was directed to the stability of the claimed invention. (Joint Brief at 21-22). The title of the particular subheading or the inclusion of other arguments do not erase the fact that, to overcome an obviousness rejection, the patentee cited the "consists essentially of" transition to demonstrate that the prior art did not teach or suggest the claimed formulation of "only enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water." (Appx117) (emphasis in original). As such, the patentee "clear[ly] and unmistakabl[y]" disavowed any additional ingredients in the formulation recited in draft claim 20 of the '008 patent. As mentioned in Alkem's answering brief, the prosecution of the parent '008 patent is highly instructive in light of the similarity between the claims of the application and those of the patents in suit. (Joint Brief at 11). Therefore, the patentee's understanding and use of "consists essentially of" in the parent patent is highly instructive as to how the Court should construe "consists essentially of" in the patents-in-suit. This understanding is reinforced throughout the prosecution history and the specification.

Azurity also claims the '008 patent recited "two separate buffer components" meaning it cannot be a disavowal of more than one buffer. (Joint Brief at 22). However, a single buffer may require more than one component, such as an acid and a base or a salt¹³—for example, citric acid and sodium citrate. Therefore, the '008 patent claims do not recite more than one "buffer" but instead they recite two ingredients that form one "buffer."

¹³ Encyclopaedia Britannica, *Buffer / chemistry* (last visited Aug. 5, 2021), <https://www.britannica.com/science/buffer-chemistry>.

Azurity also argues the prosecution history of the ‘008 patent is only instructive when the “subsequently issued patents contain the same limitation.” (Joint Brief at 23) (emphasis in original). However, *Andersen Corp. v. Fiber Composites, LLC* does not make it a requirement that the limitations be the same—this is a quote from *Elkay Mfg. Co. v. EBCO Mfg. Co.*, which *Andersen Corp.* cited for its assertion that the prosecution history of the parent is “highly instructive.” *Andersen Corp.*, 474 F.3d 1361, 1368 (Fed. Cir. 2007) (citing 192 F.3d 973, 980 (Fed. Cir. 1999)). In fact, the *Andersen Corp.* case involved claims that had “nearly identical” language as the parent application—not “the same” language. *Id.* The Court noted that throughout prosecution of the child patents, “the applicants continued to distinguish the claimed inventions from prior art references in the same manner,” which served to limit the scope of the claimed subject matter. *Id.* at 1369. Here, the patentee also distinguished the claimed inventions from prior art across both the parent and child patents that involve “nearly identical” language. (Joint Brief at 12-14).

Contrary to Azurity’s arguments, it is unmistakable that the patentee amended the claims in the ‘868 patent from “comprising” to “consisting essentially of” to exclude additional components from the formulation. Indeed, the examiner expressly required the patentee to do so. (Appx228-229). The examiner specifically directed the applicant to the “comprising” transition term and faulted the claims for not containing an “explicit proviso which would exclude the use of additional components.” *Id.* (emphasis added). The very next amendment to the claims replaced “comprising” with “consisting essentially of” to solve this flaw. (Appx245-248). Azurity does not address this express instruction from the examiner in its reply.

Azurity further faults Alkem for not identifying any case law where an amendment from “comprising” to “consisting essentially of” suggests a finding of prosecution disclaimer. (Joint Brief at 24). However, it is a general principle of claim construction that a patentee’s decision to

narrow his claim through amendment may be presumed to be a disclaimer of the territory between the original claim and the amended claim. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 740 (2002). It is undeniable that “consisting essentially of” is a narrower transition phrase than “comprising” and it is clear from the examiner’s rejection that the claims required an “explicit proviso which would exclude the use of additional components.” (Appx228-229). The only amendment to the claim language which could exclude additional components per the examiner’s direction is the patentee’s switch from the open transition term “comprising” to the “consisting essentially of” term. As mentioned in Alkem’s answering brief, an intentional narrowing can be inferred by this amendment to overcome rejection. (Joint Brief at 13).

Azurity next cites an out-of-circuit district court case for proof that amending “comprising” to “consisting essentially of” did not narrow the claims of the patent. (Joint Brief at 24). However, this case is more supportive of Alkem’s position than Azurity’s. In *Callicrate v. New Age Indus. Corp.*, the defendant argued that an amendment from “comprising” to “consisting essentially of” excluded potential examples of a “connection means” in a means-plus-function term. No. 04-4008-JAR, 2005 WL 1027095, at *10 (D. Kan. Apr. 27, 2005). Specifically, the defendant argued this amendment meant the transition term restricted the limitation so that it could only include “a wire” as opposed to “a clip, wire band, grommet or other equivalent device,” as the plaintiff proposed. *Id.* at *8. By its nature, a means-plus-function term is drafted to have a broad scope of potential “means” for performing a special function. This broad type of claim is not at issue in the present case. Furthermore, the *Callicrate* Court was able to point to the limitation that the “consisting essentially of” amendment actually restricted. Coincidentally, it restricted “a deformable **grommet**” to mean “only one grommet” to overcome a rejection based on a prior art reference that disclosed two grommets. *Id.* at *5, *10 (emphasis added). This is strikingly similar to the present

dispute and proves that an amendment from “comprising” to “consisting essentially of” can indeed operate to limit “a” to mean “only one.”

b) Alkem’s construction is the only one that could sufficiently inform any POSA of the scope of the buffer limitation.

Azurity dismisses Alkem’s multiple possible interpretations of the claim language without addressing how the specification teaches a POSA which of them would and would not be encompassed by their construction. There is no instruction in the specification on how to combine multiple different buffers in a way that would maintain the concentration and stability as required by the claims and Azurity points to none. Azurity also notes that Alkem’s ANDA contains an amount of buffer that happens to fall within the claimed concentration, but this does not automatically render the scope of the claims understandable to any POSA reading the patents.

c) The patentee understood a “citrate/phosphate buffer” as a single buffer, not a combination of buffers.

Azurity also argues that the intrinsic evidence supports a construction that encompasses multiple buffers because of the reference to a “citrate/phosphate buffer.” (Joint Brief at 26). However, the declaration of Dr. Mosher, one of the two inventors, demonstrates that the patentee considered this to only be one buffer, not a combination of buffers. In the declaration, Dr. Mosher lists the different types of buffers that he used to demonstrate the stability of the formulations: “Formulation in Table 3 were prepared using fumarate, tartrate, malate, aspartate, glycinate, lactate, formate, phthalate, acetate, succinate, gluconate, glutamate, citrate, phosphate, and citrate/phosphate buffers, respectively.” (Appx238). Listing the different buffers in this way shows that the patentee understood each listed substance to be a single, independent buffer, including a citrate/phosphate buffer. This listing was done throughout the declaration. (Appx236, 240). The separate listing also occurs in the claims as well—further demonstrating the patentee’s understanding that “citrate/phosphate” is a single buffer separate from citrate and phosphate.

Table 1 submitted along with this declaration also proves the “citrate/phosphate buffer” is its own type of singular buffer, and not a combination of buffers. (Appx236-237). If the citrate/phosphate buffer was a combination of the citrate and phosphate buffers, one would expect some combination of the two individual buffers’ compositions. But that is not what is seen in Table 1. According to Table 1, the citrate buffer contains citric acid and sodium citrate (or just citric acid in H7-H9), while the phosphate buffer contains sodium dihydrogen phosphate. (Appx 236-237). However, the citrate/phosphate buffer contains citric acid and *disodium hydrogen* phosphate, not *sodium dihydrogen* phosphate. (Appx236-237). The use of two different ingredients in the two different buffers proves that the citrate/phosphate buffer is its own type of buffer and not just a mixture of citrate and phosphate buffers.

Table 1

Ingredients	Compositions (mg/mL) for Stability		
	H1	H2	H3
	Citrate	Phosphate	Citrate/ Phosphate
Acetic acid, glacial	-	-	-
Sodium Acetate	-	-	-
Citric acid, anhydrous	1.82	-	1.07
Sodium citrate, dihydrate	0.15	-	-
Glycine	-	-	-
Sodium dihydrogen phosphate, anhydrous	-	1.2	-
Disodium hydrogen phosphate, anhydrous	-	-	0.63

(Appx236-237) (altered for Court’s convenience).

d) The “rule” regarding “a” or “an” is not applicable here.

Azurity continues to urge the Court to blindly accept the “rule” that “a” means “one or more” but neglects to address the significant flaw with the application of that “rule” noted by Alkem. (Joint Brief at 17-18). Instead, Azurity incorrectly asserts that Alkem argues “consisting essentially of” “mandates a departure” from this “rule.” (Joint Brief at 27). This mischaracterizes

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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

AZURITY PHARMACEUTICALS, INC.,

Plaintiff,

v.

ALKEM LABORATORIES LTD.

Defendant.

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C.A. No. 19-2100-LPS

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MEMORANDUM OPINION

November 16, 2021
Wilmington, Delaware

other recited ingredients in the claimed liquid solution” would be achieved. (*See* D.I. 72 at 47)

The Court sees no dispute here that would be resolved by adoption of any claim construction, including Defendant’s proposed construction.

E. “consisting essentially of”⁹

Plaintiff
Plain and ordinary meaning.
Defendant
“including, exclusively”
Court
“including the listed ingredients and open to unlisted ingredients that do not materially affect the basic and novel properties of the invention”

The Court will construe “consisting essentially of” in accordance with its well-established legal meaning, which is: “includ[ing] the listed ingredients and . . . open to unlisted ingredients that do not materially affect the basic and novel properties of the invention.” *PPG*, 156 F.3d at 1354; *see also* Manual of Patent Examining Procedure § 2111.03. As discussed above (in connection with the Court’s construction of “a buffer”), Alkem has not shown that the narrowing amendment – from “comprising” to “consisting essentially of” – means that “consisting essentially of” should be interpreted more narrowly than it is customarily understood. Nor is the Court convinced by Alkem’s citation to the common specification, which mentions that claims reciting “comprising” are open-ended. (D.I. 72 at 49-50) (citing ’868 patent at 29:35-42) Additionally, Alkem conceded at the hearing that a construction reflecting the well-established legal meaning of “consisting essentially of” would be agreeable. (*See* Tr. at 51)

III. CONCLUSION

An appropriate Order follows.

⁹ This term appears in claims 1, 13, 14, and 26 of the ’868 patent and claims 1, 19, and 30 of the ’621 patent.

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

AZURITY PHARMACEUTICALS, INC.,

Plaintiff,

v.

ALKEM LABORATORIES LTD.

Defendant.

C.A. No. 19-2100-LPS

ORDER

At Wilmington this **16th** day of **November, 2021**:

For the reasons set forth in the Memorandum Opinion issued this date,

IT IS HEREBY ORDERED that the following claim terms are construed as follows:

Claim Term	Court's Construction
a buffer	"one or more buffers"
a buffer to maintain the pH	"one or more buffers to maintain the pH"
a citrate buffer <i>[to maintain the pH about 4.5 or below comprising citric acid and sodium citrate]</i>	"one or more buffers made of citrate ions"
<i>[a buffer comprising] a mixture of citric acid and sodium citrate[, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation]</i>	No construction needed.
consisting essentially of	"including the listed ingredients and open to unlisted ingredients that do not materially affect the basic and novel properties of the invention"



UNITED STATES DISTRICT JUDGE

EXHIBIT 3

CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

AZURITY PHARMACEUTICALS, INC.,

Plaintiff,

v.

ALKEM LABORATORIES LTD.,

Defendant.

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C.A. No.: 19-2100 (MSG)

**CONFIDENTIAL –
SUBJECT TO PROTECTIVE
ORDER**

EXHIBIT 3

**DEFENDANT’S STATEMENT OF ISSUES
OF FACT THAT REMAIN TO BE LITIGATED**

CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

on the basic and novel characteristics of the claim and therefore take Alkem's ANDA Product outside the scope of the Asserted Claims of the '621 Patent.

VII. THE ASSERTED CLAIMS ARE INVALID UNDER 35 U.S.C. § 103

205. Alkem's purported non-infringement arguments fail to rebut Azurity's case that Alkem's ANDA Product infringes the Asserted Claims.

A. Prior Art**i. U.S. Patent No. 8,568,747 (“the '747 Patent”)**

206. The '747 Patent issued October 29, 2013 and is entitled “Enalapril Compositions.” It is prior art to the Asserted Patents under 35 U.S.C. 102(a)(1).

207. The '747 patent explains that a significant segment of the consuming public has difficulty swallowing tablets, which can lead to noncompliance, and tablets are not always recommended for children and the elderly. ('747 patent at 4:68-5:15). The '747 patent aimed to address those issues, among others, by providing for “stable enalapril oral liquid compositions as well as enalapril powder compositions for oral liquid administration.” (*Id.* at 5:28-32.) After identifying various concentrations of enalapril and mannitol in disclosed embodiments, the '747 patent describes embodiments of the claimed invention to include commonly known excipients, including, without limitation buffering agents, preservatives and sweeteners before noting that additional common excipients were contemplated and citing to widely known, highly regarded treatises such as Remington: The Science and Practice of Pharmacy, Remington's Pharmaceutical Sciences, Pharmaceutical Dosage Forms and Pharmaceutical Dosage forms and Drug Delivery Systems, which the '747 patent expressly “incorporated by reference.” (*Id.* at 7:11-9:36). The '747 patent also teaches the use of buffering agents to “maintain the pH.” (*Id.* at 7:17-41.) The '747 patent teaches the use of colloidal silicon dioxide despite acknowledging its reported effect of reducing enalapril's stability. (*Id.* at 10:12-22.)

EXHIBIT 3**CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

208. The '747 patent teaches that the liquid formulations claimed and described therein are “stable,” which the '747 patent explains refers to “enalapril oral liquid compositions having at least about 90% enalapril and 5% or less total impurities or substances at the end of a given storage period” that is not otherwise defined. (*Id.* at 13:4-10.) The '747 Patent discloses, “[a]t refrigerated and ambient conditions, in some embodiments, the enalapril oral liquid compositions described [in the '747 patent] are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, or at least 36 weeks.” (*Id.* at 13:29-33.) The '747 patent includes examples of oral liquid enalapril formulations that are stable, without the addition of preservatives or buffering agents, even if a person of ordinary skill in the art would understand the stability of the claimed formulations to be of limited duration.

ii. September 2014 Package Insert for Epaned® (enalapril) for Oral Solution (“the Epaned Insert”)

209. The Epaned Kit Product (Epaned Powder for Oral Solution, which contains 150 mg of enalapril maleate in a 150 mL bottle, to be reconstituted with 150 mL of ORA-SWEET® SF provided) was approved for commercial marketing in 2013 under NDA No. 204308. (Epaned Kit Approval Letter, ALK_ENPL_00258781.)

210. The Epaned® Kit Product was approved for commercial marketing in 2013 under NDA No. 204308.

211. Silvergate launched the Epaned® Kit Product in October of 2013.

212. The Epaned Kit Product is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

213. The Epaned Kit Product Insert (“Epaned Insert”) describes the Epaned Kit Product as follows:

EXHIBIT 3

CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

EPANED Powder for Oral Solution is a kit consisting of 1 bottle containing a dry powder blend of enalapril maleate, USP, mannitol, and colloidal silicon dioxide and 1 bottle of Ora-Sweet SF diluent for reconstitution resulting in a 1 mg/mL EPANED oral solution. The Ora- Sweet SF diluent contains: purified water, glycerin, sorbitol, sodium saccharin, xanthan gum, and flavoring. Buffered with citric acid and sodium citrate. Preserved with methylparaben (0.03%), propylparaben (0.008%), and potassium sorbate (0.1%).

(Epaned Insert, §11.)

214. The Epaned Insert notes, “Enalapril has been evaluated for safety in more than 10,000 patients, including over 1,000 patients treated for more than one year.” (Epaned Insert § 6.1.)

215. The Epaned Insert describes the formulation to include a citric acid/sodium citrate buffering composition and paraben preservatives:

EPANED Powder for Oral Solution is a kit consisting of 1 bottle containing a dry powder blend of enalapril maleate, USP, mannitol, and colloidal silicon dioxide and 1 bottle of Ora-Sweet SF diluent for reconstitution resulting in a 1 mg/mL EPANED oral solution. The Ora- Sweet SF diluent contains: purified water, glycerin, sorbitol, sodium saccharin, xanthan gum, and flavoring. Buffered with citric acid and sodium citrate. Preserved with methylparaben (0.03%), propylparaben (0.008%), and potassium sorbate (0.1%).

(Epaned Insert, §11.)

216. The Epaned Insert is prior art to the Asserted Claims under 35 U.S.C. § 102(a)(1).

217. The Epaned Insert provided persons of ordinary skill in the art with a clear starting point for formulating enalapril maleate into a stable solution that would not require a reconstitution step prior to administration, including providing for preservatives and a citric acid/sodium citrate buffering solution. Moreover, the Epaned Insert bolsters the notion that enalapril could be effective in formulations using one or more parabens as a preservative.

218. There exist two separate Epaned® products. One product, “RTU Epaned® Oral Solution” throughout this report referring to the product that is the subject of NDA

EXHIBIT 3**CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

208686(https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=208686#32978), and which is the subject of this lawsuit. This product contains as the preservative sodium benzoate. Dr. Mahan refers to the product in his report simply as “Epaned®.”

219. The other Epaned® product, referred to by Alkem’s experts as “Epaned® For Solution,” the product that is the subject of NDA 204308 (https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=204308#17015), a product produced as a powder that is reconstituted by addition of liquid vehicle. This product contains as the preservative a mixture of parabens and is not listed in the Orange Book as covered by either the ’482 or ’621 patents, and is not the subject of this lawsuit. Azurity’s expert refer to this product as the “Epaned Kit.”

iii. Allen, Jr., L., and Erickson III, M., Stability of Alprazolam, Chloroquine Phosphate, Cisapride, Enalapril Maleate, and Hydralazine Hydrochloride in Extemporaneously Compounded Oral Liquids, 55 Am. J. Health-Syst. Pharm., at 1915-20 (Sep. 15, 1998) (“Allen”)

220. Allen is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

221. Allen is a peer-reviewed publication from the American Journal of Health-System Pharmacy.

222. The authors studied the chemical stability of several drugs including Enalapril Maleate in extemporaneously compounded oral liquids. Allen discloses detailed information on the stability of 1 mg/mL Enalapril Maleate in aqueous solutions and its pH and temperature dependence. Allen also teaches that the pH of an Enalapril Maleate solution would differ depending upon the liquid with which the drug is mixed. Allen specifically states that the Enalapril Maleate solutions “were stable in three oral liquids compounded extemporaneously from sweetened vehicles and tablets for 60 days when stored without light at 5 and 25° C.” (*Id.* at 1919).

EXHIBIT 3

CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

iv. Boukarim, C., et al., Preservatives in Liquid Pharmaceutical Preparations, 9 J. Appl. Res. 1&2, at 14-17 (2009) (“Boukarim”)

223. Boukarim is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

224. Boukarim is a peer-reviewed publication from the Journal of Applied Research.

225. Boukarim (Defendants' Invalidity Contention- Exhibit 4; SLVGT_RTU_00011171 – SLVGT_RTU_00011174) broadly discusses the use and justification of preservatives in liquid pharmaceutical preparations, which “are particularly susceptible to microbial growth because of the nature of their ingredients. Such preparations are protected by the addition of preservatives that prevent the alteration and degradation of the product formulation.” (*Id.* at 14.) Boukarim adds, “Among the most commonly used preservatives in the conservation of liquid pharmaceutical preparations are sodium benzoate, potassium sorbate, and methyl hydroxybenzoate (methylparaben).” (*Id.* at 14). Boukarim highlights the high amount of preservatives that may be found in some liquid pharmaceutical preparations.” (*Id.* at 17.) This observation can be linked to the statement in the Abstract of the Boukarim publication that preservatives can be utilized to “intentionally extend the shelf-life” of liquid pharmaceutical products.

226. A POSA would have been motivated by the teachings of Boukarim to utilize one or more commonly used preservatives with liquid pharmaceutical preparations, including sodium benzoate and/or one or more parabens, for improving the stability and extending the shelf-life of Enalapril Maleate oral liquid formulations.

v. Casas, M., et al., Physicochemical Stability of Captopril and Enalapril Extemporaneous Formulations for Pediatric Patients, 20 Pharm. Dev. & Tech. 3, at 271-78 (Published online Nov. 26, 2013) (“Casas”)

227. Casas is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

228. Casa is a peer-reviewed publication from Pharmaceutical Development and Technology.

CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

229. Casas (Defendants' Invalidity Contention- Exhibit 5; SLVGT_RTU_00011175 – SLVGT_RTU_00011182) discloses the development and physicochemical stability of oral liquid extemporaneous formulations of the antihypertensive drugs Captopril and Enalapril, emphasizing the advantages of liquid formulations to adjust the dose and frequency to pediatric patients, thus improving patient compliance. (Casas at 271.) The Enalapril formulations in Casas, included a buffering solution but no preservative, and the pH was maintained slightly more acidic than the pH of around 3 known to result in maximal stability for Enalapril. (Casas at 275.) Although this conclusion is consistent with what was already known in the art as of the Casas publication date, it would have, nevertheless, motivated a POSA to formulate Enalapril Maleate in liquid solutions using buffering agents and preservatives to maintain the pH of around 3 to maximize the drug product stability and commercial viability.

230. In reference to the temperature effect on the stability of the investigated oral liquid solutions according to the ICH Guidelines, Casas discloses that these solutions were “more stable at 5° C than at the upper temperatures” and noted that, “[f]or enalapril PEF, the drug content was above the 95% until 50 days of study for 5° and 25° C, decreasing below this value only in the case of 40° C.” (*Id.* at 277.) These observations are consistent with what was already known in the art on the stability of liquid dosage forms as presented in a comprehensive review article. (Glass, B.D and Haywood. A., *Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products*. J. Pharm. Pharmaceut. Sci. (2006) 9:398-426) (“Glass”). From the investigation of 83 liquid formulations reported in the literature as of 2006, stability considerations were of a concern for only 7.2% of these liquid dosage forms. Among the investigated 83 stable liquid dosage forms was enalapril maleate. The stability of enalapril maleate 1 mg/ml extemporaneous liquid formulations from the investigated three compounding vehicles

EXHIBIT 3**CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

reported in the ‘Allen’ prior art that is cited as reference #83 in the “Glass” review article, is summarized in Table 1. on p. 405 “1mg/mL mixture stored in the dark was stable for 60 days at 5 and 25° C”.

- vi. *Sosnowska, K., et al., Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared from Commercially Available Tablets, 66 Acta Poloniae Pharmaceutica—Drug Research 3, at 321-26 (2009) (“Sosnowska”)*

231. Sosnowska is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

232. Sosnowska is a peer-reviewed publication from Acta Poloniae – Drug Research.

233. Sosnowska (Defendants' Invalidity Contention- Exhibit 6; ALK_ENPL_00258616 – ALK_ENPL_00258621), first provide an overview of Enalapril Maleate and its use in pediatric cardiology and some of the drawbacks of the powder formulations when mixed with liquid foods, such as accuracy of measurement, not easy to administer and unpleasant taste. (Sosnowska at 321.) Sosnowska identifies a number of factors when the task is to prepare liquid formulations, emphasizing the significance of formulation stability. Sosnowska teaches that liquid enalapril maleate formulations can be stabilizing by modifying the pH using a buffering system and can include one or more preservatives. (Sosnowska at 325.)

- vii. *Nahata, M., et al., Stability of Enalapril Maleate in Three Extemporaneously Prepared Oral Liquids, 55 Am. J. Health-Syst. Pharm. At 1155-57 (June 1, 1998) (“Nahata”)*

234. Nahata is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

235. Nahata is a peer-reviewed publication from the American Journal of Health-System Pharmacists.

236. Nahata (Defendants' Invalidity Contention- Exhibit 7; SLVGT_RTU_00011183 – SLVGT_RTU_00011185) points out upfront that that “[no] liquid formulation form [of enalapril maleate] is commercially available for pediatric patients (Nahata at 1155), thus, establishing the

EXHIBIT 3**CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

motivation to develop this formulation in order to address a medical and market need. Nahata makes reference to previous stability data with enalapril maleate pointing to the fact that there are no known stability data for enalapril in readily available vehicles such as carboxymethylcellulose in syrup. Nahata presents the rationale of the study by explaining that, “Our study was designed to determine the stability of enalapril maleate in deionized water, citrate buffer solution, and a sweetened suspending agent at 4 and 25° C.” (*Id.* at 1156.) Nahata discloses that at 4° C, all of the enalapril formulations retained >94% of the initial concentration throughout the 91-day study period. (*Id.*) Nahata states that whereas at 25° C enalapril mixed with deionized water retained >90% of the initial concentration for only 56 days, enalapril mixed with the citrate buffer solution and with the sweetened suspending agent maintained >92% of the initial concentration for the full 91-day period, thus, providing further motivation to the POSA to stabilize liquid enalapril solutions with a citrate buffer and would ease concerns about the effect of flavoring on the drug’s stability.

237. Nahata concludes the discussion of the study by noting the following: Because of the lack of stability data, some doses of enalapril maleate have been dispensed as a powder prepared by diluting crushed tablets with lactose. This practice is cumbersome and labor-intensive, however. The knowledge that enalapril maleate is stable in widely available vehicles should simplify the preparation and delivery of weight-specific doses to infants and young children.

viii. Rippley, R., et al., Pharmacokinetic Assessment of an Oral Enalapril Suspension for Use in Children, 21 Biopharmaceutics & Drug Disposition at 339-44 (2000) (“Rippley”)

238. Rippley is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

239. Rippley is a peer-reviewed publication from Biopharmaceutics & Drug Disposition.

240. Rippley (Defendants' Invalidity Contention- Exhibit 8; SLVGT_RTU_00008364 – SLVGT_RTU_00008369) contains many teachings similar to those discussed in connection with

EXHIBIT 3**CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

other prior art references cited above, however, Rippley also establishes that the liquid formulations tested were stable and equally bioavailable as the then-commercialized tablets, thus, linking the liquid formulation's stability to its in vivo performance, i.e. bioavailability. Rippley concludes:

An enalapril suspension preparation with documented stability and known bioavailability is now available and has been used in clinical studies in children and infants with hypertension. This enalapril suspension provides for greater ease and individualization of dosing in pediatric patients. In addition, the similarity of enalapril suspensions to marketed tablets will provide chronically treated pediatric patients with the flexibility to change formulations over time.

(Rippley at p. 344 last paragraph.)

ix. U.S. Patent Application Publication No. 2006/0121066 A1 Sucralose Formulations to Mask Unpleasant Tastes (“the ’066 Publication”)

241. The ’066 Publication is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

242. The ’066 Publication (Defendants' Invalidity Contention- Exhibit 9; SLVGT_RTU_00011215 - SLVGT_RTU_00011225) discloses taste masking methods using sucralose to mask the taste of bitter drugs. A person of ordinary skill in the art would be motivated to mask enalapril's known bitter taste using one or more sweeteners, including specifically sucralose.

243. As stated in the Abstract of the ’006 Publication:

The present invention is directed to a pharmaceutically acceptable taste masking liquid excipient base for administration of a relatively large amount of unpleasant tasting medicines. More particularly, the enhanced Sweetness and taste masking effect are produced by the addition of Sucralose to the excipient base with maintenance of a pH from about 2 to about 5. The invention is further directed to medicinal compositions comprising such a liquid excipient base and unpleasant tasting medicines. Still further, the invention is directed to a method for taste masking unpleasant tasting medicines through their incorporation into the claimed liquid excipient bases.

CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

('066 Publication, Abstract.)

244. The '006 Publication, in the specification under Formulations, in the Examples of Tables 4 through Table 9, it discloses the use of citric acid and sodium citrate as buffering agent and sodium benzoate as a preservative, motivating the POSA to use these excipients in oral liquid preparations of other drugs, including cardiovascular drugs, such as Enalapril.

x. *Strickley, Robert G., et al., Pediatric Drugs—A Review of Commercially Available Oral Formulations, J. Pharm. Sci., [97] 1731-1774 (May 2008) (“Strickley”)*

245. Strickley is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

246. Strickley is a peer-reviewed publication from the Journal of Pharmaceutical Sciences.

247. Strickley (ALK_ENPL_00257873 – ALK_ENPL_00257916; SLVGT_RTU_00009614 – SLVGT_RTU_00009657) provides a comprehensive review of commercially available oral formulations of pediatric drugs as of 2007. Strickley emphasizes both the regulatory incentives and clinical challenges to develop oral formulations for pediatric patients, which are required to have a measurable dosage form to administer based upon body weight, and also an acceptable taste-masking for children. Formulation selection is based on the physicochemical and organoleptic properties of the active drug substance such as solubility, chemical stability, and taste along with the targeted dose. Strickley further explains:

oral pediatric formulations are available in 17 different varieties and can be either a ready-to-use formulation such as a solution, syrup, suspension, tablet, scored tablet, chewable tablet, orally disintegrating tablet, or thin strip, or can also be a formulation that requires manipulation such as a powder for constitution to a suspension, tablet for constitution to a suspension, powder for constitution to a solution, drops for reconstitution to a suspension, concentrated solution for dilution, effervescent tablet, bulk oral granules, bulk oral powder, or solid in a capsule to

EXHIBIT 3**CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

mix with food or drink. Recently there has been an increase in pediatric formulation development inspired by increased regulatory incentives.

(Strickley, at Abstract.)

248. Table 1 in Strickley lists “Excipients Used in Pediatric Formulations,” whereas the identified “Ready to Use or Required Manipulation of Selected Listings of Commercially Available Pediatric Oral Formulations” are comprehensively presented in Table 2 and Table 3, respectively. Strickley states in the Abstractt, “The intent of this review is to educate the reader on the various types of formulations administered orally to pediatrics, the rationale in deciding which type of formulation to develop, the excipients used, development challenges, the in-use handling of oral pediatric formulations, and the regulatory incentives.”

249. In Table 2, Strickley discloses the Inactives in Formulation (as listed in Package Insert or PDR) of commercially available ready-to-use oral liquid solution formulations of various drugs incorporating citric acid and sodium citrate as buffer and sodium benzoate or methylparaben and propylparaben as preservatives and which can be stored at room temperature unlike the Epaned oral solution which requires to be refrigerated. Room temperature storage is certainly more challenging to achieve but advantageous from a product development, commercialization and marketing perspectives. The Strickley review is a valuable source of guidance to those involved in the development of oral pediatric formulations, including oral liquid solutions, and would have certainly motivated the POSA having the task to develop a stable, bioavailable, safe and efficacious oral liquid formulation of Enalapril Maleate.

xi. International Patent Application Publication No. WO 2017/077425 A1 Oral Solution of ACE Inhibitor (“WO ’425”) Priority Date: 7 November 2015

250. WO ’425 is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

EXHIBIT 3**CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

251. The priority date of the WO '425 which is the date of the original filing of the international patent application is November 7, 2015 which is earlier to the priority date of the '482 and '621 patents which is March 18, 2016.

252. The WO '425 discloses oral solution compositions of ACE Inhibitor and more specifically lisinopril dihydrate with improved stability and improved palatability. It emphasizes the importance of drug-excipient interactions and incompatibilities with certain pharmaceutical excipients which lead to drug degradation by various mechanisms. "Lisinopril upon contact with some pharmaceutical excipients is converted into cyclized degradation product, lisinopril diketopiperazine. Further, lisinopril also get degraded by hydrolysis of side chain ester group or oxidation. It was surprisingly found that the combination of lisinopril and preservative in solution form results in enhanced stability ACE inhibitor, lisinopril toward cyclization, hydrolysis and oxidation." (WO '425 at 4.)

253. Example 1 in WO '425 disclosed the use of sucralose as a sweetener and methylparaben and ethylparaben as preservatives.

xii. *FDA Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products (2003) ("FDA Stability Guidance")*

254. FDA Stability Guidance is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

xiii. *The Handbook of Pharmaceutical Excipients (6th ed. 2009) ("HPE")*

255. HPE is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1).

xiv. *Remington: The Science and Practice of Pharmacy, 745–75 (21st ed. 2006) ("Remington")*

256. Remington is prior art to the Asserted Patents under 35 U.S.C. § 35 102(a)(1).

EXHIBIT 3

CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

- xv. *World Health Organization, WHO Expert Committee on Specifications for Pharmaceutical Preparations, 46 WHO Technical Report Series 970 (2012) (“WHO Report”)*

257. WHO Report is prior art to the Asserted Patents under 35 U.S.C. § 35 102(a)(1).

- xvi. *de Villiers, Melgardt, Buffers and pH Adjusting Agents, Ch. 18 in “A Practical Guide to Contemporary Pharmacy Practice” (Judith E. Thomson, ed., Lppincott, Williams & Wilkins, 3rd ed. 2009)(“de Villiers”)*

258. de Villiers is prior art to the Asserted Patents under 35 U.S.C. § 35 102(a)(1).

B. Motivation to Combine or Modify

259. As discussed throughout the prior art analysis above, each piece of prior art includes teachings that would motivate a drug formulator to seek out the other relevant prior art and modify the teachings therein with a reasonable expectation of arriving at the claimed inventions. At the time of the effective filing date for the patents-in-suit, the U.S. market for safe, effective anti-hypertensive drugs would have provided ample motivation for a person of ordinary skill in the art to try to improve upon the enalapril options then available by formulating an enalapril maleate ready-to-use solution that eliminated the need to reconstitute the drug from powder formulations in connection with administration and to maximize its economic potential by creating and marketing a long-lasting, stable, orally dosed liquid enalapril maleate formulation that cardiac patients would consume especially pediatric patients..

260. Further motivation to combine references explanation appears above, in my description of the prior art, and in my Detailed Analysis, below. It should also be added that a motivation for a POSA to combine prior art references is the fact that complimentary teachings can be found in the prior art references. The '747 patent, Epaned Insert and Allen address formulation development and testing areas that are specific to enalapril /enalapril maleate whereas, de Villiers and Boukarim broadly address the areas of Buffers & pH Adjusting Agents and

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

- - -

AZURITY PHARMACEUTICALS, INC.,	:	CIVIL NO. 19-2100
	:	
Plaintiff	:	
	:	
	:	
	:	
	:	
v.	:	
	:	
	:	
	:	
ALKEM LABORATORIES, LTD.,	:	Philadelphia, Pennsylvania
	:	July 29, 2022
Defendant	:	1:01 p.m.

- - -

TRANSCRIPT OF PRETRIAL HEARING
HELD VIA TELECONFERENCE
BEFORE THE HONORABLE MITCHELL S. GOLDBERG
UNITED STATES DISTRICT COURT JUDGE

- - -

APPEARANCES:

For the Plaintiff: T.O. KONG, ESQUIRE
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One Market Plaza
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San Francisco, CA 94105

For the Defendant: TIMOTHY H. KRATZ, ESQUIRE
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609-440-2177

1 THE COURT: Okay. And when you say "by
2 deposition," you're going to introduce their
3 testimony --

4 MR. KONG: Correct.

5 THE COURT: -- by transcript, right? Or
6 are you going to ask me to watch a video?

7 MR. KONG: Well, that's one of our
8 questions for Your Honor. Would you prefer video or
9 would you prefer it be read into the record? I think
10 by the time we get to trial, frankly, we'll have
11 probably about 30 to 45 minutes of video time, so it
12 shouldn't be that long. But if Your Honor prefer --

13 THE COURT: Okay.

14 MR. KONG: -- that we read it, we're more
15 than happy to.

16 THE COURT: I'll leave it up to you. If
17 it's not too long, it's up to you, okay?

18 MR. KONG: Understood.

19 THE COURT: Okay. And then your expert,
20 you have one expert, Dr. Little?

21 MR. KONG: We have two experts. One is Dr.
22 Little. He is a formulator. These inventions are
23 pharmaceutical formulations, and he is a formulator
24 who will testify regarding both infringements by
25 Alkem, and also, he'll be rebutting the affirmative

1 defenses that defendants are putting forward here.

2 THE COURT: Yes.

3 MR. KONG: Second, we have Dr. Mayhan (ph).
4 He's a pediatric nephrologist. He will be testifying
5 regarding the long-felt need for these products. So
6 he's an actual physician who is on the ground
7 treating patients who experienced the past several
8 decades prior to the invention. He can explain what
9 that was like from his perspective in terms of the
10 challenges presented by the existing therapies and
11 how this invention addresses the long-felt need
12 presented by those -- the problems presented by those
13 existing therapies.

14 THE COURT: Okay. I read this and I forgot
15 how this was laid out. So it's going to go -- are we
16 going to -- is your preference to do everything
17 that's related to infringement, both sides, that is
18 plaintiffs talk about infringement with their
19 witnesses, then we go to the defendant's witnesses,
20 they talk about infringement, then we come back to
21 you? Then we turn to defendant on invalidity, or we
22 just -- we just do plaintiff's entire case, then
23 defendant's entire case, and those issues are covered
24 in each side of the case? Is my -- I don't think I
25 asked that question very clearly. Do you understand

1 what I'm asking you, Mr. Kong?

2 MR. KONG: I got you.

3 THE COURT: Okay.

4 MR. KONG: So I think that the parties have
5 agreed in paragraph 27, which is on page 5, as to the
6 order of proof. And what will happen is we'll
7 present first on infringement, defendants will then
8 rebut that, and then we shift to their affirmative
9 defenses. And so then they'll put on their witnesses
10 on invalidity, and then we'll put on our rebuttal
11 witnesses. And so I think the only witness, given
12 that format, who would testify twice is Dr. Little
13 because I mentioned that he's testifying on both
14 infringement for plaintiff and also rebutting
15 defendant's invalidity case.

16 THE COURT: Right.

17 MR. KONG: So we asked him to testify on
18 day 1 on infringement, and then probably on day 3 in
19 rebuttal to their infringement -- I'm sorry, their
20 invalidity case.

21 THE COURT: All right.

22 MR. KONG: So --

23 THE COURT: Well, I'm basically -- if you
24 all can work it out to the convenience of your
25 witnesses and how you want to do it, don't worry

1 about me. I'm happy to accommodate, you know,
2 whatever order you want to -- you want to present the
3 witnesses. I'm not going to be too much of a
4 stickler as to, you know, how you do it. So you
5 decide. If you can't -- if you can't agree, then
6 I'll weigh in, okay?

7 MR. KONG: Very good.

8 THE COURT: All right. All right, and so
9 on Exhibit 7 is defendant's -- let's see, Exhibit 7,
10 defendant's witnesses, yes? So you have --

11 MR. KRATZ: That's correct, Your Honor.

12 THE COURT: You're going to start with your
13 fact witness, please, Mr. Kratz? Do you want to just
14 give me a quick overview?

15 MR. KRATZ: Sure, Your Honor. The fact
16 witnesses are also by deposition, and we share Mr.
17 Kong's opinion that we can do that however you want.
18 I think we probably have less than 30 to 45 minutes
19 of video. There are two of the inventors, and then
20 there's another witness that's a -- has been
21 designated by both sides. It's an additional
22 witness. So those are the fact witnesses. We do not
23 have a live fact witness. The only live fact witness
24 was designated by plaintiffs, Backlov.

25 THE COURT: Okay.

1 MR. KRATZ: And so our live witnesses will
2 be our experts, and I can talk about them briefly if
3 you'd like.

4 THE COURT: Go ahead.

5 MR. KRATZ: Yes. So we have two experts,
6 Barrett Rabinoe (ph). He may also be -- under the
7 way we've structured the order of presentation, he
8 may also be testifying twice because he's an
9 infringement expert, but he also is a rebuttal expert
10 for secondary considerations, so just like Dr.
11 Little. And then both plaintiffs and defendants can
12 sort that out as to, you know, whether we want to
13 have them both testify twice or figure out some other
14 alternative. We -- I'm sure the parties can figure
15 that out and then help the Court. The other expert
16 is Dr. Constantinitus (ph), and he is our invalidity
17 expert.

18 THE COURT: Okay. All right. A couple --
19 a couple things came to mind. Regarding exhibits,
20 however you want to do it, that is whether you want
21 to do it before a witness testifies or in the
22 beginning of your case or whenever -- and this is I
23 guess more pertinent to live witnesses, but I want --
24 and the lawyers can get together if you haven't done
25 it already. Plaintiff is to tell defense all the

1 exhibits that you propose to introduce, and defense
2 is to do the same for plaintiff. I will not accept
3 any exhibits in the record that aren't connected to
4 and tethered to a witness, or if it (indiscernible)
5 by -- it can come in by stipulation, but it has to
6 pertain to an issue in the case. So either it's
7 connected to a witness or it pertains to -- directly
8 pertains to an issue in the case. And I'm just
9 trying to keep the record as uncluttered as possible.
10 And I will ask you -- I'm not -- you're not going to
11 get a verdict from me, you know, when we -- I'm going
12 to, you know, review the record and write an opinion.
13 So if you want to use any -- I'll ask you to make
14 submission at the end. Once we have the record
15 complete regarding exhibits, and if you refer to an
16 exhibit in your briefs, you're going to have to again
17 connect it to why it's outcome-determinative as to --
18 as it relates to infringement or invalidity. Again,
19 all designed to keep, you know, exhibits at a
20 manageable level.

21 So let's get the exhibits together and what
22 you want to introduce, and let's get them introduced,
23 if there is by agreement, beforehand. I find that
24 that really saves -- I know that most of the live
25 witnesses are experts, but it saves a lot of "Judge,

1 may I approach? Here's Plaintiff's Exhibit 45. Do
2 you know what that is? Is it authentic?" Blah,
3 blah, blah, blah, blah. If it's in evidence already
4 and we do that before a witnesses, even as to
5 questioning about it, you don't have to go through it
6 because we'll already have it introduced in advance.
7 If there's exhibits that there's objections to, then
8 we'll just take them as the objections arise. We'll,
9 you know, do it old school, and you'll tell me why it
10 shouldn't come in.

11 I presume, but I'll say that, you know,
12 I'll have an exhibit binder. Please have one for my
13 law clerk, whose name is Owen Healy, who is on the
14 call here, and then a separate binder that we're
15 going to keep as part of the -- you know, the
16 official record that will go if there's an appeal.
17 So for us, I guess three binders per side.

18 Any questions on exhibits from you, Mr.
19 Kong?

20 MR. KONG: Just one brief followup. And so
21 I assume what we'll be doing or at least what we have
22 in mind is we'll be providing exhibits on a witness-
23 by-witness basis to the Court? So before a witness
24 testifies, we'll walk up with three copies of the
25 binder?

1 THE COURT: Yes.

2 MR. KONG: And --

3 THE COURT: Whatever is -- whatever is
4 easiest for you. And, you know, just as long as I
5 have it in front of me. If you want to use it so I
6 can, you know, look at it in conjunction with your
7 questioning, but whatever is easiest for you.

8 MR. KONG: And then I imagine the only
9 thing that's not addressed by this is cross-
10 examination. If a document comes up that's maybe not
11 on the exhibit list, we can deal with that on the
12 fly?

13 THE COURT: Yes, that's fine. Yes, that
14 works.

15 MR. KONG: Very good. Thank you.

16 THE COURT: Mr. Kratz, are you good with
17 that process?

18 MR. KRATZ: Absolutely.

19 THE COURT: Okay. Okay. You'll tell me --
20 and I'll ask, but just so you know, if there is an
21 agreement that an expert witness is qualified, on
22 direct, you could lead them through their
23 qualifications or you can direct me to the CV. And
24 of course the other side reserves its right to ask
25 questions about qualifications. I know there's an

1 issue as to one witness. And I think, Mr. Kratz, we
2 can raise that -- we'll get to that in a second. And
3 then it would be great if you could, and I'm
4 instructing you to, get your -- get together and get
5 a -- if you can, a larger list of uncontested facts,
6 otherwise known as stipulations. And we can get
7 those introduced at the beginning of the trial so we
8 can make use of those. Try to -- try to get as many
9 uncontested facts, you know, as you can. I mean
10 there were a few I noted that were contested that
11 seemed to me to be, you know, sort of obvious that
12 they were going to be uncontested, but I don't want
13 to go through those right now. But the longer the
14 uncontested facts are, if you have one pristine
15 document that I can have, my law clerk can have, and
16 that we can introduce into the record, that makes
17 things easier.

18 I will hear opening statements even though
19 it's a bench trial. Not too long. You know, if you
20 can explain your case to me, I think that would be --
21 that would be useful. So -- and to the extent that
22 you need to do a type of tutorial on your product,
23 you can -- I assume the lawyers can do that. It
24 doesn't seem like the products are that complicated.
25 So you can explain to me your different -- your

1 different clients' products during your opening. Are
2 you all good with that? Mr. Kong, any comments on
3 that process?

4 MR. KONG: Good with us, Your Honor. Just
5 to be clear, so not too long, 30 to 45 minutes, in
6 that range?

7 THE COURT: Yes.

8 MR. KONG: Maybe up to an hour?

9 THE COURT: Yes. I'm not -- I'm not going
10 to be a stickler for time unless I feel you're
11 starting to repeat or dealing with topics that are --
12 I don't think are, you know, worthwhile. I'll ask
13 you why you're doing it and, you know, if it starts
14 to become a -- if you're not efficient, then I'll
15 start to care about time. If you're efficient, then
16 I won't and I'll let you try your case. So let's see
17 what happens. Okay?

18 MR. KONG: Understood, Your Honor.

19 THE COURT: I don't -- I can't imagine why
20 you need an hour opening, but maybe you do. I don't
21 understand the case well enough.

22 MR. KONG: I agree (indiscernible).

23 THE COURT: Yes, so let's see how it goes.
24 In other words, the lawyers get the benefit of the
25 doubt until I feel like you're wasting our time. And

1 then I'll -- then we'll talk about that and if I'm
2 right, I'll start to get a little more prickly about
3 time, but not at the outset, okay?

4 MR. KONG: Very good.

5 THE COURT: All right. So as to all those
6 topics, the uncontested facts and qualifying
7 witnesses, Mr. Kratz, any comments on any of that,
8 what I said?

9 MR. KRATZ: No comments. It's understood,
10 and we will follow those directions.

11 THE COURT: Okay. What -- Mr. Kratz, while
12 I have you, what's your -- what's your motion? Give
13 me a thumbnail of what your issue is?

14 MR. KRATZ: I'll turn it over to George
15 Barry, my partner for that, but just to give you the
16 context of it, it is -- we are attempting to exclude
17 the witness, Dr. Mayhan. And it's not a
18 qualification issue per se, but it is where his
19 support fits into the case. This is an unusual case
20 in a way because there is no branded product that
21 practices the patents, and so the secondary
22 considerations, which is what Dr. Mayhan's report
23 goes toward, is trickier than would otherwise be
24 apparent in the case where you had a practicing
25 entity. But I -- it's George's motion, and I would

1 like to, you know, turn it over to him to the extent
2 that you have any questions (indiscernible).

3 THE COURT: Okay. Mr. Barry, I'm not --
4 I'll hear from you, but I don't want -- I don't want
5 to hear and decide this now for reasons I said at the
6 outset, which is I want to understand the case
7 better. Your partner, Mr. Kratz, said it related to
8 review of a report -- or I guess Dr. Mayhan's report,
9 which I really haven't read. So let's table this
10 until I can hear the openings, hear a couple
11 witnesses, and then you'll let me know -- the lawyers
12 will let me know when it's, you know, appropriate,
13 when we're getting close to Mayhan's testimony, and
14 then, you know, hopefully I'll have better context
15 and I'll be able to understand what you want to say,
16 Mr. Barry, okay? Does that work?

17 MR. BARRY: That's fine, Your Honor. Thank
18 you.

19 THE COURT: Okay. All right, that's really
20 all I can think of on, you know, my things I wanted
21 to talk about. Mr. Kong, is there anything you want
22 to cover, logistics, details? Anything is on the
23 table, it's fine.

24 MR. KONG: Yeah, Your Honor mentioned
25 opening statements. I wanted to raise closing

1 arguments and see if Your Honor wanted to have them
2 or reserve them for a point later in time.

3 THE COURT: I don't know. I mean I think
4 in these -- in the Hatch-Waxman trials I've done, we
5 reserve them. We sort of -- I think -- I reserve my
6 right to change my mind. I think that it's probably
7 best to -- for us to sort of get a draft opinion
8 together in our head and really, really get as on top
9 of this as we can, and then, you know, have sort of
10 mini closing arguments then as we're really focused.
11 But maybe, I'm not sure. But it's a bench trial, so
12 if I decide, you know, half hour closings, then I'm
13 sure the lawyers will be more than capable of putting
14 them together without, you know, much notice. Okay?
15 So I don't know. Probably not until after I get to
16 review the record, but we'll see, okay?

17 MR. KONG: Fair enough. And then one last
18 issue I wanted to raise, Your Honor, is we didn't
19 receive a 282 notice from defendants in this case,
20 and so --

21 THE COURT: A what?

22 MR. KONG: So there's a statute, 35 USC
23 282(c). It's been on the books for a while. It
24 requires a defendant in a patent case to provide
25 written notice at least 30 days in advance of trial

1 regarding the prior art they're relying on at trial
2 and information relating to that prior art. And what
3 the statute says is that in the absence of a 282
4 notice, proof of those matters may not be made at
5 trial unless the Court holds otherwise. So 30 days
6 in this case was passed on July 18, and Alkem did not
7 send us anything on July 18 or since then.

8 So the concern is that it's not clear to us
9 if Alkem is going to try to rely on prior art that's
10 outside of their expert reports. I --

11 THE COURT: No, they're not going to --
12 they're not going to be allowed to do that.

13 MR. KONG: Okay.

14 THE COURT: There's no surprises. I mean,
15 you know --

16 MR. KONG: I appreciate that --

17 THE COURT: -- unless --

18 MR. KONG: -- confirmation, Your Honor. I
19 just -- I read in their statement of facts that
20 remain to be litigated, there is a piece of prior art
21 that's not in any of their expert reports. I just
22 want to make sure we're clear that nothing gets in
23 that's not in their expert reports in terms of prior
24 art.

25 THE COURT: Well, generally, without -- and

1 I'll let Mr. Kratz talk to it. There's not going to
2 be any ambush or surprises. So far, my impression of
3 Mr. Kratz is that he wouldn't -- he's not going to
4 take that strategy. But, Mr. Kratz, do you want to
5 respond to what Mr. Kong said?

6 MR. KRATZ: Well, typically, with respect
7 to Mr. Kong to -- they're not shy to have raised that
8 with us, that the prior art that they think that
9 we're springing on them in our statement of facts,
10 we'll take a look at it. But as a general rule, Your
11 Honor, we absolutely are not intending to spring
12 surprises on the Court. The prior art that we're
13 relying on in the expert report was disclosed long
14 ago and were repeated again throughout the pretrial
15 order. So, you know, we --

16 THE COURT: Okay.

17 MR. KRATZ: We commit to creating no
18 surprise at least with respect to the prior art in
19 the case.

20 THE COURT: Got it.

21 MR. KRATZ: And --

22 THE COURT: Okay.

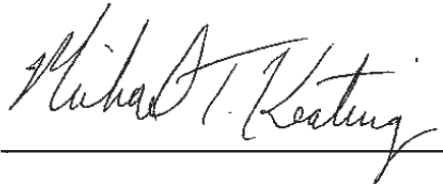
23 MR. KRATZ: And if there is a particular
24 reference that plaintiff is concerned about, I'd be
25 happy to discuss it with them (indiscernible) --

CERTIFICATION

I, Michael Keating, do hereby certify that
the foregoing is a true and correct transcript from the
electronic sound recordings of the proceedings in the
above-captioned matter.

8/1/22

Date



Michael Keating

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC.,)	
)	
Plaintiff,)	
)	
v.)	C.A. No. 19-2100 (MSG)
)	
ALKEM LABORATORIES LTD.,)	CONFIDENTIAL –
)	FILED UNDER SEAL
Defendant.)	

AMENDED EXHIBIT 1 TO
[PROPOSED] FINAL PRETRIAL ORDER

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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

AZURITY PHARMACEUTICALS, INC.,	:	
	:	
	:	
<i>Plaintiff,</i>	:	C.A. No.: 19-2100 (MSG)
	:	
v.	:	
	:	
ALKEM LABORATORIES LTD.,	:	
	:	
<i>Defendant.</i>	:	
	:	

EXHIBIT 1

**PLAINTIFF'S AND DEFENDANT'S
JOINT STATEMENT OF UNCONTESTED FACTS**

I. PARTIES

1. Plaintiff Azurity Pharmaceuticals, Inc. (“Azurity”), formerly Silvergate Pharmaceuticals, Inc. (“Silvergate”), is a corporation organized and existing under the laws of the State of Delaware with a principal place of business at 8 Cabot Road, Suite 2000, Woburn, MA 01801.

2. Defendant Alkem Laboratories, Ltd. (“Alkem”) is an Indian corporation having a place of business at Devashish Building, Alkem House, Senapati Bapat Road, Lower Parel, Mumbai – 400 013, India.

II. ENALAPRIL AND EPANED[®]

A. Enalapril

3. The active ingredient in the formulations of the Asserted Claims is enalapril.

4. Enalapril maleate tablets for oral administration were approved by FDA in 1985 and marketed under the trade name Vasotec[®].

B. Epaned[®]

5. Azurity is the holder of New Drug Application (“NDA”) No. 208686 for the oral liquid medication known by the trade name Epaned[®].

6. The active ingredient of Epaned[®] is enalapril maleate.

7. Epaned[®] is approved by the U.S. Food and Drug Administration (“FDA”).

8. Epaned[®] is an angiotensin converting enzyme (“ACE”) inhibitor administered as a ready-to-use oral solution.

9. Epaned[®] is indicated for the treatment of hypertension in adults and children older than one month to lower blood pressure.

10. Epaned[®] is indicated for the treatment of symptomatic heart failure.

EXHIBIT 1
CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

11. Epaned® is indicated for the treatment of asymptomatic left ventricular dysfunction, to decrease the rate of development of overt heart failure, and reduce hospitalization for heart failure.

12. On September 20, 2016, FDA approved NDA No. 208686 as an oral solution for, among other things, treatment of pediatric and adult hypertension.

III. ASSERTED PATENTS

A. U.S. Patent No. 10,786,482

13. United States Patent No. 10,786,482 (the “’482 patent”), entitled “Enalapril Formulations,” issued on September 29, 2020, from U.S. Patent Application No. 16/177,159, which was filed October 31, 2018.

14. Gerold L. Mosher and David W. Miles are named as inventors of the ’482 patent.

15. The ’482 patent claims priority to provisional U.S. Patent Application No. 62/310,198, which was filed March 18, 2016.

16. Azurity owns the ’482 patent.

17. Azurity asserts that Alkem’s ANDA product infringes claims 16, 18, 22, 23, and 28 of the ’482 patent, all of which depend from claim 14.

18. Claim 14 claims “[a]n oral liquid formulation, comprising:

- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
- (iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens; and
- (iv) water;

EXHIBIT 1
CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

42. Alkem's ANDA product contains 0.25 mg/mL mixed berry flavor as a flavoring agent.
43. Alkem's ANDA product contains water.
44. Alkem's ANDA product does not contain mannitol.
45. Alkem's ANDA product does not contain silicon dioxide.
46. Alkem's ANDA product has a pH below 4.5.
47. Alkem's ANDA product has a pH between about 3 and about 3.5.
48. Alkem's ANDA product has a pH of about 3.3.

VI. ALKEM'S DEFENSES

49. Alkem asserts Azurity cannot prove Alkem's ANDA product meets each of the limitations of the Asserted Claims.

50. Alkem asserts that the Asserted Claims are invalid for improper inventorship, as obvious pursuant to 35 U.S.C. § 103 and/or as failing to satisfy the definiteness, written description and/or enablement requirements set forth in 35 U.S.C. § 112.

VII. PRIOR ART TO THE ASSERTED CLAIMS

51. U.S. Patent No. 8,568,747 ("747 patent") issued October 19, 2013, and is titled "Enalapril Compositions." The '747 patent is prior art to the Asserted Claims under 35 U.S.C. § 102(a)(1). The '747 patent was before the USPTO during prosecution of the Asserted Patents.

52. The Epaned Kit Product Insert ("Epaned Insert") published September 2014, describes the Epaned Kit Product as follows:

EPANED Powder for Oral Solution is a kit consisting of 1 bottle containing a dry powder blend of enalapril maleate, USP, mannitol, and colloidal silicon dioxide and 1 bottle of Ora-Sweet SF diluent for reconstitution resulting in a 1 mg/mL EPANED oral solution. The Ora-Sweet SF diluent contains: purified water, glycerin, sorbitol, sodium saccharin, xanthan gum, and flavoring. Buffered

EXHIBIT 1
CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

with citric acid and sodium citrate. Preserved with methylparaben (0.03%), propylparaben (0.008%), and potassium sorbate (0.1%).

Epaned Insert, §11.

53. The Epaned Insert is prior art to the Asserted Claims under 35 U.S.C. § 102(a)(1).

54. Allen, et al., *Stability of Alprazolam, Chloroquine Phosphate, Cisapride, Enalapril Maleate, and Hydralazine Hydrochloride in Extemporaneously Compounded Oral Liquids*, 55 Am. J. Health-System Pharm. 1915 (1998) (“Allen”) is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1). Allen was before the USPTO during prosecution of the Asserted Patents.

55. Boukarim, et al., *Preservatives in Liquid Pharmaceutical Preparations*, Journal of Applied Research, Vol. 9, No.1 & 2, at 14–17 (2009) (“Boukarim”) is prior art to the Asserted Patents under 35 U.S.C. § 102(a)(1). Boukarim was before the USPTO during prosecution of the Asserted Patents.

56. Casas, M., et al., *Physicochemical Stability of Captopril and Enalapril Extemporaneous Formulations for Pediatric Patients*, 20 Pharm. Dev. & Tech. 3, at 271-78 (Published online Nov. 26, 2013) (“Casas”) is prior art to the Asserted Claims under 35 U.S.C. § 102(a)(1). Casas was before the USPTO during prosecution of the Asserted Patents.

57. Sosnowska, K., et al., *Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared from Commercially Available Tablets*, 66 Acta Poloniae Pharmaceutica—Drug Research 3, at 321-26 (2009) (“Sosnowska”) is prior art to the Asserted Claims under 35 U.S.C. § 102(a)(1). Sosnowska was before the USPTO during prosecution of the Asserted Patents.

58. Nahata, M., et al., *Stability of Enalapril Maleate in Three Extemporaneously Prepared Oral Liquids*, 55 Am. J. Health-Syst. Pharm. at 1155-57 (1998) (“Nahata”) is prior art

EXHIBIT 1
CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

to the Asserted Claims under 35 U.S.C. § 102(a)(1). Nahata was before the USPTO during prosecution of the Asserted Patents.

59. Rippley, R., et al., *Pharmacokinetic Assessment of an Oral Enalapril Suspension for Use in Children*, 21 Biopharmaceutics & Drug Disposition at 339-44 (2000) (“Rippley”) is prior art to the Asserted Claims under 35 U.S.C. § 102(a)(1). Rippley was before the USPTO during prosecution of the Asserted Patents.

60. U.S. Patent Application Publication No. 2006/0121066 A1 Sucralose Formulations to Mask Unpleasant Tastes (“’066 Application”), published on June 8, 2006, is prior art to the Asserted Claims under 35 U.S.C. § 102(a)(1). ’066 Application was before the USPTO during prosecution of the Asserted Patents.

61. Strickley, Robert G., et al., *Pediatric Drugs—A Review of Commercially Available Oral Formulations*, 97 J. Pharm. Sci. at 1731-1774 (2008) (“Strickley”) is prior art to the Asserted Claims under 35 U.S.C. § 102(a)(1).

62. International Patent Application Publication No. WO 2017/077425 (“WO ’425”) is prior art to the Asserted Claims under 35 U.S.C. § 102(a)(1).

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC.,)
)
-----Plaintiff,)
) Case No.
vs.) 19-2100-MSG
)
ALKEM LABORATORIES LTD.,)
) Volume I
-----Defendant.)

TRANSCRIPT OF BENCH TRIAL

BENCH TRIAL had before the Honorable
Mitchell S. Goldberg, U.S.D.C.J., in Courtroom
4B on the 16th of August, 2022.

APPEARANCES

MORRIS NICHOLS ARSHT & TUNNELL LLP
BY: MEGAN DELLINGER, ESQ.

-and-

WILSON SONSINI GOODRICH & ROSATI
BY: T.O. KONG, ESQ.
WENDY DEVINE, ESQ.
TINA HANSON, ESQ.
EVAN SUMNER, ESQ.
JODY KAROL, ESQ.
JESSICA RAMSEY, ESQ.

Counsel for Plaintiff

1 pediatric, specific pediatric medicine to the
2 overlooked pediatric population.

3 Q. How did Silvergate become Azurity?

4 A. We met at an -- at an industry meeting. We had
5 discussions with CutisPharma, and through those
6 discussions we discovered that Silvergate was
7 focused on the pediatric area and CutisPharma
8 was focused more on the geriatric patient
9 population. And we discovered through that
10 conversation that there were many similarities
11 with overlooked patient populations where
12 appropriate drug formulations were not
13 available to those -- to those patient
14 populations. And we thought that because of
15 this we thought it would be good to merge the
16 companies and combine them, and we did that in
17 May of 2019 when we became Azurity
18 Pharmaceuticals.

19 Q. Have you heard this morning some discussion
20 about Epaned?

21 A. (No audible response.)

22 Q. Can you tell us, what is Azurity's Epaned as
23 it's on the market today?

24 A. Azurity's Epaned is a ready-to-use liquid
25 formulation to treat hypertension.

1 Q. Is it approved for use in children?

2 A. It's approved for use in children.

3 Q. And does Azurity's Epaned fit into that vision
4 that you had with Silvergate when you founded
5 the company?

6 A. Absolutely.

7 Q. You mentioned that it's a ready-to-use
8 formulation. What do you mean by "ready to
9 use"?

10 A. Ready to use means that you can take the
11 product from the pharmacy shelf and provide it
12 directly to the patient without any kind of
13 manipulation in between to prepare the
14 formulation and that that product will remain
15 stable for at least 12 months.

16 Q. How long does it need to be stable for that to
17 happen?

18 A. It has to be stable for at least 12 months.

19 Q. From manufacture?

20 A. Yes.

21 Q. And why does it need that level of stability?

22 A. The distributors, the drug distributors in the
23 country, the three main distributors, Cardinal
24 Health, AmerisourceBergen and ABC will not
25 typically accept a drug product with less than

1 12 months of dating, 12 months of stability
2 because of the time it takes to move through
3 the distribution chain.

4 Q. What happens if Azurity ships the product and
5 it expires? It goes beyond the shelf life
6 before it gets to a patient?

7 A. If it gets to the pharmacy and expires, the
8 pharmacy returns it to the distributor. The
9 distributor returns it to Azurity. We refund
10 or credit that, and then the product is
11 destroyed.

12 Q. Epaned kit has been mentioned this morning. Do
13 you know what Epaned kit is?

14 A. I do.

15 Q. What is it?

16 A. Epaned kit was a reconstitutable powder that
17 provided enalapril maleate in a liquid form for
18 children.

19 Q. Were you involved in the development of the
20 Epaned kit?

21 A. I was.

22 Q. And were there any issues associated with
23 Epaned kit?

24 A. It was a reconstitutable powder. So it came in
25 a kit with a bottle of powder and a diluent,

1 and you had to combine that diluent. Once that
2 was combined, the product was only stable for
3 60 days in the liquid form.

4 Q. Did you originally set out to make a 60-day
5 stable product?

6 A. Originally we had hoped to obtain 90 days of
7 stability on the reconstituted product because
8 that's very typically what the mail order
9 pharmacies will dispense, a 90-day supply, but
10 we were unable to get to 90-day stability.

11 Q. Did you ever -- are you aware of any examples
12 of any sort of safety issues associated with
13 Epaned kit or complaints about Epaned kit?

14 A. Well, we -- we had a number of complaints that
15 came in with the kit associated with
16 preparation and -- and the -- sort of the
17 operations within the pharmacy where
18 contamination, which turned out to be fibers
19 from the pharmacy technician's sweater got into
20 the product during reconstitution. We had
21 examples of someone taking a Bic pen and trying
22 to poke it through the induction seal and the
23 powder, and the cap came off. And they
24 reported that the cap was in the powder when
25 they received it, but the investigation yielded

1 that they had punched that through. A number
2 of fiber issues and we had a case where a
3 pharmacy technician didn't use the diluent that
4 we provided in the kit but took the diluent off
5 the shelf of the pharmacy and added it to the
6 bottle and there was too much diluent in it and
7 another case where there was not enough
8 diluent, same kind of reason. So there were
9 various issues that were associated with
10 pharmacy technicians preparing the kit in the
11 pharmacy before dispensing it to the patient.

12 Q. What's the result if the diluent is not placed
13 in the powder correctly?

14 A. So it changes the concentration of the drug
15 that's available. So the dose of the drug
16 changes and potentially has a safety
17 implication for the patient.

18 Q. Before Epaned kit how were enalapril oral
19 liquid formulations made?

20 A. They were available either as a tablet or as a
21 compounded liquid that was made in the
22 pharmacy.

23 Q. And do you believe that Epaned kit was safer
24 than compounding?

25 A. I do believe the Epaned kit was absolutely

1 Dr. Little, what do the '482 and '621
2 patents discuss?

3 A. Generally, they discuss stable liquid
4 formulations of the active pharmaceutical
5 ingredient enalapril.

6 Q. Do the '482 and '621 patents share the same
7 substitutions?

8 A. They do.

9 Q. Can we have PDX 103, please.

10 Dr. Little, would you please explain to
11 us what enalapril is?

12 A. Sure. Your Honor will see the big organic
13 structure on the right-hand side, that's the
14 molecule itself. I will refer to it a little
15 bit just nontechnically and to the extent I get
16 into technical details I'll try to explain the
17 best I can. On the left-hand side I just
18 mention some things about the molecule. It is
19 what's called an ACE inhibitor, which is an
20 Angiotensin-converting enzyme. It's used for
21 treatment, among other things, of hypertension.
22 One thing that is important to recognize about
23 this molecule that's important for this case is
24 it's what's called prodrug. It's the drug
25 before the drug is the way to think about it.

1 That molecule that you're seeing on your screen
2 right there is not what's called
3 pharmacologically active. In other words, if
4 that molecule hit a target in vivo it would not
5 do the function that the real drug would it has
6 to be converted in order to do that.

7 THE COURT: What are the
8 manifestations of hypertension in infants?

9 THE WITNESS: I'm not a doctor in
10 that area.

11 THE COURT: Generally, I'm not going
12 to hold you to it. When I think of
13 hypertension I think of elderly patients, I
14 don't really think of pediatric patients.

15 THE WITNESS: In terms of pediatric
16 patients I couldn't speak to the differences.

17 THE COURT: You can explain.

18 MS. DEVINE: A lot of pediatric
19 patients with hypertension have kidney failure
20 or kidney disease which leads to hypertension
21 as a secondary problem. So we actually have an
22 M.D. who will testify later and I'm sure will
23 tell me I'm wrong about everything. But it can
24 lead to rapid heart rate. It can lead to all
25 sorts of things.

1 THE COURT: How does it manifest, how
2 do you know? Is it a high pulse rate, bad
3 blood pressure, what is it?

4 MS. DEVINE: High blood pressure.

5 THE COURT: High blood pressure. I
6 just wanted a general background. It's not
7 outcome determinative for the case. Just for
8 my education.

9 MS. DEVINE: Could we go to PDX 104?

10 BY MS. DEVINE:

11 Q. And, Dr. Little, would you please explain to us
12 what you were referencing about enalapril being
13 a prodrug?

14 A. Sure. So the molecules on the prior slide that
15 Your Honor saw is here. That's enalapril, and
16 the conversion of that drug to the drug on the
17 right which is enalaprilat -- we'll talk about
18 this throughout the week -- is the conversion
19 that leads to a pharmacologically active agent.
20 The way that that occurs is by a reaction
21 that's called hydrolysis. Now, this occurs
22 rapidly in the liver. But what's important to
23 recognize is that hydrolysis occurs by this
24 bond right here, and this is called an ester
25 bond. That bond is very susceptible to water

1 to break it.

2 So what's important to realize here about
3 the prodrug is that this form, the reason why
4 you don't administer the form that is active
5 already is that this form has very good
6 absorption in the gastrointestinal tract. So
7 it will move from your gut, the stomach, into
8 the bloodstream whereas this guy right here
9 will not. So you want the conversion to happen
10 after it goes into the body. In other words,
11 you don't want this in your tube.

12 THE COURT: What's the term
13 "prodrug"?

14 THE WITNESS: Prodrug is the before
15 the drug. So it's the drug that sits on the
16 shelf. It's the drug that's readily absorbed
17 in the human body, but then it has to convert
18 into something else. Another commonly thought
19 of as a prodrug, is, you know, Your Honor has
20 heard a lot about the COVID vaccine. Those are
21 genetic materials. Those are prodrugs. The
22 translation of that genetic material into
23 proteins in the body is the drug itself. So
24 the genetic material is the prodrug.

25 BY MS. DEVINE:

1 Q. When was enalapril first available as a
2 treatment?

3 A. In the 1980s. It was a tablet form. It was
4 called Vasotec.

5 Q. And as a tablet form, was that dosage form
6 acceptable for all patient populations?

7 A. Not all patient populations, especially elderly
8 and children would have -- especially infants
9 would not be able swallow the pill.

10 Q. And in general in a situation like that, how
11 would that be addressed?

12 A. Well, what would be addressed would be
13 extemporaneous compounding, so what would
14 happen is a pharmacist in a hospital or in a
15 pharmacy would take the tablet and crush it
16 typically with a mortar and pestle and would
17 solubilize or suspend whatever the contents
18 were of that tablet and then try to ensure the
19 proper dosage, purity, et cetera, in order to
20 administer to the patient population that can't
21 take the pill.

22 Q. Are there challenges from a formulation
23 perspective with doing that with a drug like
24 enalapril?

25 A. Yes, there is.

1 Q. What are those challenges?

2 A. Well, there's a number of them. There's going
3 to be, for instance, possibility of there being
4 contamination whenever you compound. There can
5 be differences in how it's compounded from
6 pharmacy to pharmacy, and there can be
7 differences in what the pharmacy used. So, for
8 instance, the liquid that is used, the
9 substances within the liquid that are called
10 excipients, these all can be different. So
11 what you can have is sometimes wildly different
12 at least in the formulations.

13 Q. In general, is it a problem to put enalapril in
14 water?

15 A. Yeah, it is. As I was referring back to in
16 this particular case, although this reaction
17 occurs fast inside the body, again, you do not
18 want the agent on the right-hand side to be in
19 your water bottle that you're going to be
20 administering or the tube you're administering.
21 Water rapidly will hydrolyze ester bonds and it
22 depends on the molecule how much that happens,
23 but it's dangerous. So if you're going to take
24 this thing and you're going to surround it with
25 water, you're creating a situation where

1 degradation products can occur, and that's
2 particularly difficult for long-term stable
3 formulations.

4 MS. DEVINE: Can we go to PDX 105,
5 please? Can we skip to the next one? Thank
6 you.

7 BY MS. DEVINE:

8 Q. I think you told us about the first one. Could
9 you tell us what you're depicting on this slide
10 and talk through it for me.

11 A. Sure. This is just a time line that I created.
12 On the left-hand side is the compounding stage
13 for this particular medication, and I mentioned
14 some of these issues here on the left-hand side
15 in the answer to the last question, I think,
16 come from compounding.

17 Once that period came to be about the
18 2013 time frame, the Epaned kit was released.
19 So what the kit is, is for solution or for oral
20 solution. So what that means is that the
21 powder that you would reconstitute with the
22 liquid. That's better because everything is
23 all preset. The pharmacists are supposed to be
24 using the same liquid, but they don't sometimes
25 and they're supposed to be reconstituting

1 according to a particular schedule, which
2 doesn't happen all the time but at least
3 there's strict instructions for how to
4 reconstitute it. That eliminates a large
5 amount of the human error. There's still some,
6 but it eliminates that.

7 Once it's reconstituted, however, it's
8 not intended always for long-term stability.
9 So it can have short-term stability problems,
10 and there's still an issue possibly with
11 contamination when you're adding things
12 together.

13 MS. DEVINE: Can we have PDX 105,
14 please?

15 BY MS. DEVINE:

16 Q. And what came after the kit?

17 A. What came after the kit is what Your Honor has
18 heard so far as the solution or the
19 ready-to-use liquid. What that is, it's
20 already all mixed up so there's no more issues
21 with human error and contamination related
22 issues, but it's all made according to what's
23 called current good manufacturing practices by
24 the United States Food and Drug Administration
25 that enforces it.

1 MS. DEVINE: Now, could we go to PDX
2 108, please.

3 BY MS. DEVINE:

4 Q. Did you formulate understanding of who a person
5 of skill in the art is for forming your
6 opinion?

7 A. Yes, I did.

8 Q. What is that?

9 A. So my opinion is that it would be somebody with
10 a PhD in formulation relevant pharmaceutical
11 science, chemistry or a similar subject with
12 minimal post-degree experience in formulating
13 pharmaceutical products. Alternatively there
14 could be a lesser degree of education, like a
15 bachelor's degree, pharmacy, pharmaceutical
16 science, chemistry or a similar subject with at
17 least five years practical experience in
18 formulating pharmaceutical products.

19 I also put forth that a person of
20 ordinary skill in the art would also have
21 experience with pharmaceutical excipients as
22 applied to their selection and use in drug
23 formulations.

24 Q. Is a biologist a similar subject?

25 A. It could be if that person has the relevant

1 experience in the field.

2 Q. Have you reviewed the opinions of Dr. --
3 Alkem's expert, Dr. Rabinow, regarding
4 infringement?

5 A. Yes, I have.

6 Q. And did you review his definition of a person
7 of skill in the art?

8 A. I did.

9 Q. Do you agree with that definition?

10 A. I don't, but if I were to adopt his definition
11 it would not change my opinions.

12 Q. Do you agree with Dr. Rabinow that a medical
13 doctor would be part of the team collaborating
14 with a person of skill in the art?

15 A. I do. I believe that we would work with
16 medical doctors when formulating products.

17 MS. DEVINE: Can we get PDX 109,
18 please.

19 BY MS. DEVINE:

20 Q. In forming your opinions, did you apply the
21 definitions of claim terms set by the Court?

22 A. Yes, I did.

23 Q. What are those?

24 A. I included them here on the slide for the claim
25 term "about." I applied the definition of

1 quantitative portion of the composition you can
2 see this column, it says milligram per
3 milliliter, right here, and that says
4 1.000 milligram per milliliter which is between
5 about 0.6 to about 1.2 milligram per
6 milliliter.

7 Q. What is the next limitation?

8 A. It is number two which is a buffer comprising a
9 mixture of citric acid and sodium citrate
10 wherein the buffer is present in concentration
11 between about 5 millimolar and about 20
12 millimolar in the oral liquid formulation.

13 Q. Does Alkem's ANDA product meet that limitation?

14 A. It does. So the next two rows down on the
15 right-hand side you will citric acid anhydrous
16 and sodium citrate anhydrous. And the amount
17 of those ingredients are listed in the
18 milligram per milliliter column as 1.820 and
19 0.150 respectively. You can add those together
20 and you can convert them to the units of the
21 claim. This is milligram per milliliter, this
22 is going to be moles, millimoles. So you have
23 to convert that.

24 Q. Let's pull up PDX 112, please.

25 Could you just tell us what's the

1 difference between a milligram per millimeter
2 and then millimole?

3 A. Sure, so the standard unit of weight is gram,
4 that's weight, the mass of something. What a
5 mole is, is it's the number of things, and each
6 one of those things has a particular weight and
7 you get that through the mass. So citric acid
8 in this case is a bit smaller, weighs a bit
9 less, whereas sodium citrate is a bit bigger,
10 mainly because it has a sodium attached to it.
11 So you can use these values to convert from the
12 weight to the number of them. Millimole is a
13 concentration based on moles versus milligrams
14 being a concentration based on weight. So
15 whenever you do this calculation and add them
16 together at the bottom you will see that the
17 total of the buffer concentration is 10.054
18 millimolar.

19 Q. Let's go back to the claim language in the
20 chart. Does that value that you calculated
21 fall within the concentration in the claim?

22 A. Yes, it does. The value I just read off was
23 between about 5 millimolar and about 20
24 millimolar.

25 Q. What is the next limitation?

1 storage period of at least 18 months at about
2 five degrees plus or minus three degrees
3 Celsius.

4 Q. As we just discussed with the stability data
5 does Alkem's ANDA product meet that claim
6 limitation?

7 A. It does.

8 Q. Let's look at the last claim, claim 28.

9 What does that require?

10 A. It adds an additional limitation to claim 14,
11 wherein the buffer is present at a
12 concentration between about 10 millimolar and
13 about 20 millimolar in the oral liquid
14 formulation.

15 Q. And from your calculation earlier does Alkem's
16 ANDA product have that concentration?

17 A. It does.

18 Q. In your opinion, does Alkem's product meet each
19 of the limitations of the asserted claims of
20 the '482 patent?

21 A. It does.

22 MS. DEVINE: Your Honor, I'm about to
23 move on. I'm conscious of -- I don't know when
24 you want me to break.

25 THE COURT: Move on to the next

1 Q. Dr. --

2 THE COURT: Give me a second. Go
3 ahead.

4 BY MS. DEVINE:

5 Q. What does the specification state regarding
6 parabens in combination with sugars and sugar
7 alcohol?

8 A. Sure. What Your Honor is looking at in column
9 13 there in this one section is the portion of
10 the patent that mentions this. So the title of
11 this section is sweetener and preservative
12 incompatibility, and the section will become
13 clear what is being communicated. Let me just
14 read it. It says that "Paraben preservatives
15 especially methyl paraben can react with
16 selected sugars," and it lists several sugars,
17 "and sugar alcohols," and it lists several
18 sugar alcohols, "to form transesterification
19 reaction products. This can be undesirable
20 from a formulation and stability standpoint as
21 the transesterification creates additional
22 degradents."

23 Q. Now, Dr. Little, the title states "Sweetener
24 and Preservative Incompatibility." Do you see
25 that?

1 A. I do.

2 Q. So is -- does that mean to you as a person of
3 skill reading this patent that the paragraph is
4 necessarily stating that there are
5 incompatibilities?

6 A. No. It's clear from the context of the
7 paragraph that there can be incompatibilities.
8 And that makes sense because a formulator, when
9 reading this, is going to be looking for things
10 when they formulate things that can react.
11 Those things that could react may be in very
12 small amounts or they may react and they may
13 not be an issue in the formulation. If they
14 react to a large degree or if there's a
15 particular issue with that reaction product,
16 there could be an incompatibility which would
17 lead to the product not being viable.

18 Q. Does the specification teach you that
19 transesterification products always form?

20 A. No, it does not.

21 Q. Does the specification identify any toxicity
22 issue resulting from the possibility of
23 transesterification reactions?

24 A. No. There's no mention of that at all.

25 Q. So let's go back to the claims, and let's blow

1 Q. And did you see any discussion in the
2 prosecution history regarding the
3 transesterification products?

4 A. No. There's no discussion of it.

5 Q. Does Dr. Rabinow cite any other references
6 regarding this supposed toxicity concern?

7 A. He does, and I reviewed those references. It's
8 my opinion from reviewing those references that
9 there aren't safety concerns discussed for
10 these particular reaction products that we're
11 discussing.

12 Q. Does Alkem's ANDA product contain a sugar
13 alcohol and parabens?

14 A. It does. It contains a mixture of parabens,
15 and it contains xylitol.

16 Q. Did Alkem report to FDA any concerns or issues
17 associated with those excipients in its
18 product?

19 A. No, it did not report a concern to the FDA, but
20 more than that, prior to formulation of their
21 product, they did not identify it as something
22 that they would be even looking for. It wasn't
23 a concern at the beginning of the study.

24 Q. As a person of skill in the art, after reading
25 these patents, would you understand the

1 specification to teach away from or disclose
2 toxicity issues with formulations containing
3 parabens and sugar alcohols?

4 A. No, I would not.

5 Q. Do you believe there is actually a toxicity
6 concern associated with parabens and sugars or
7 sugar alcohols?

8 A. No, I do not. I've seen no evidence to point
9 to that, and again the specification
10 specifically says that it could be an issue but
11 will not always be an issue.

12 Q. So why do you think the inventors included that
13 information about parabens and sugars or sugar
14 alcohols in the discussion of the invention?

15 A. I just think as formulators we're looking
16 for -- when we formulate, we're looking for
17 possibilities of things reacting and ultimately
18 looking for the possibility of an interaction.
19 So I think what the inventors are doing is
20 pointing out that that's one of the places that
21 you would potentially look to find it.

22 MS. DEVINE: Your Honor, just for
23 your information, I'm going to move on to the
24 next patent if that's all right with you.

25 THE COURT: Give me a second. So

1 that?

2 A. I don't.

3 Q. Let's pull up PTX 60, again. And let's go to
4 page 455 and let's blow up the paragraph at the
5 bottom.

6 THE COURT: What is this?

7 MS. DEVINE: It's a portion of the
8 ANDA.

9 BY MS. DEVINE:

10 Q. Dr. Little, what does Alkem's ANDA state about
11 the addition of sodium hydroxide and
12 hydrochloric acid?

13 A. That it's optional as required. So what it
14 states is that if the pH is not obtained within
15 the limit of 3.0 to 3.6 you would add the pH
16 adjusting agent which is sodium hydroxide or
17 hydrochloric acid.

18 Q. And does it require the addition of sodium
19 hydroxide or hydrochloric acid?

20 A. It does not.

21 Q. Can we go back to the chart of that we were
22 looking at earlier from Alkem's ANDA claim and
23 blow up the information on the bottom of the
24 chart, please.

25 What does that chart that we were talking

1 MS. DEVINE: Correct.

2 THE COURT: Is that what you're?

3 THE WITNESS: We are. The exhibit
4 batches that are submitted to the FDA are
5 representative of the product.

6 BY MS. DEVINE:

7 Q. And have you seen any evidence that sodium
8 hydroxide has been added in making Alkem's ANDA
9 product?

10 A. There were exhibit batches where sodium
11 hydroxide was added.

12 Q. Let's say that sodium hydroxide is included,
13 does that mean that in the bottle of Alkem ANDA
14 product there is sodium hydroxide?

15 A. No, there's not. I can explain why.

16 Sodium hydroxide is what's called a
17 strong base. So what that means is that
18 whenever you put it into a solution it
19 completely dissociates or the sodium and the
20 hydroxide come apart in the solution. Those
21 portions of the original molecule will then
22 combine with other ingredients, the sodium will
23 go on to the citrate to form sodium citrate,
24 the water or the OH will attach to a hydrogen
25 ion and turn to water. So when you add sodium

1 hydroxide it turns into the other claimed
2 elements.

3 THE COURT: So why would you add it?

4 THE WITNESS: You would add it
5 because of the possibility that you'd not be in
6 the pH range as we saw in Alkem's product. So
7 if you're not within the pH range you would add
8 it to get to the pH range but if you're within
9 the pH range you wouldn't need to add it.

10 THE COURT: When would you make that
11 determination when you're in the pH range or
12 not?

13 THE WITNESS: During the formulation
14 before the product is final. So while you're
15 making it you can test the pH and if it's not
16 where the range is that you would want you can
17 make that adjustment and then when the product
18 sits on the shelf it has the pH that you
19 created but it no longer has sodium hydroxide
20 in it.

21 THE COURT: I guess I want to better
22 understand. Regarding the hydroxide.

23 THE WITNESS: Sodium hydroxide.

24 THE COURT: At what point before you
25 submit the ANDA are you using this?

1 THE WITNESS: You're using it in the
2 manufacturing stage prior to obtaining a final
3 pH that you're reporting to the FDA for the
4 exhibit batch.

5 THE COURT: Okay.

6 BY MS. DEVINE:

7 Q. Could we put up PDX 115, please.

8 Not to belabor the point but, Dr. Little,
9 do you want to explain what you put on the
10 demonstrative?

11 A. This is a representation of what I was trying
12 to explain before without the slide, but I
13 created a slide here to show it. These are the
14 claim elements and as Your Honor remembers I
15 went through and shows how each of those are in
16 Alkem's ANDA. The sodium hydroxide if it
17 needed to be added which it doesn't always need
18 to be, but if it needs to be added it's in
19 green here, it will dissociate, the sodium will
20 go here and the hydroxide ion will ultimately
21 turn into water here. So when added, if it's
22 added, it turns into the claimed elements.

23 Q. So it is possible to make Alkem's ANDA product
24 within the specifications submitted to FDA
25 without adding either hydrochloric acid or

1 A. I do remember the phrase, yes.

2 Q. Okay. So am I correct that you're not here
3 today testifying that the introduction of
4 sodium hydroxide doesn't affect the basic novel
5 properties of invention, or are you making
6 that?

7 A. It's my opinion that it doesn't affect the
8 basic novel properties. The primary reason is
9 it's not there in the final product.

10 Q. And we'll get that and I'll actually ask you
11 about that, but there's a whole lot of
12 testimony that I didn't hear today. And I just
13 want to be clear that you're saying it's not
14 there and you're also saying it's optional.

15 A. Correct.

16 Q. And those are your arguments today why the
17 introduction of sodium hydroxide doesn't mean
18 that the '621 patent does not infringe?

19 A. Could you please repeat your last question? I
20 didn't follow it.

21 Q. Those two arguments that they're not there in
22 the final product when you look at it on the
23 shelf and that it's optional are the two
24 arguments you're making regarding why the
25 possibility of introduction of sodium hydroxide

1 doesn't mean that our product does not
2 infringe. There are some double negatives
3 there, but I want to be clear those are the two
4 arguments you're making.

5 A. I think I understand -- I think I understand
6 your opinion, but I would say that it's my
7 opinion that it doesn't affect the basic and
8 novel properties.

9 Q. Are you making that argument here today?

10 A. It's my opinion.

11 Q. And you understand that the reason why that
12 assessment of affecting the basic and novel
13 properties is because of the construction of
14 the '621 patent and I know that's a legal
15 thing, but that's why that phrase is part of
16 the case?

17 A. Yes. It's based on Your Honor's construction
18 of the "consisting essentially of" term.

19 Q. If I understand correctly, the basic and novel
20 properties of this invention, of the '621
21 patent, in your opinion, is stability of the
22 formulation?

23 A. The unexpected stability of the formulation,
24 yes.

25 Q. Okay. So we're talking about stability as it

1 Barrett, B, as in boy, A, double R, E, double
2 T. Rabinow, R-A-B, as in boy, I-N-O-W.

3 THE CLERK: Do you swear or affirm
4 the testimony you give to the Court will be the
5 truth, the whole truth, and nothing but the
6 truth?

7 THE WITNESS: I do so affirm.

8 THE CLERK: Thank you. Be seated.
9 This right here is your microphone.

10 MR. HOGAN: May I begin?

11 THE COURT: Just give me a second.
12 Okay. Who are you?

13 MR. HOGAN: Mike Hogan, Your Honor,
14 for Defendant Alkem.

15 THE COURT: Good afternoon.

16 MR. HOGAN: Good afternoon.

17 THE COURT: The witness has been
18 sworn. This is Dr. Rabinow, and he's going to
19 be offered as an expert in what field?

20 MR. HOGAN: Expert in pharmaceutical
21 formulation, particularly liquid formulation.

22 THE COURT: To offer an opinion as
23 to?

24 MR. HOGAN: As to noninfringement,
25 Your Honor.

1 THE COURT: Is there any quibble from
2 the plaintiff as to his level of expertise
3 which would allow him to offer that opinion in
4 that field?

5 MR. KONG: We don't object to the
6 designation.

7 THE COURT: All right. So same thing
8 I said with Plaintiff's counsel for their
9 expert. You can leave the qualifications. You
10 don't have to. It's up to you. But they don't
11 contest that he's qualified.

12 MR. HOGAN: I would like to go
13 through his publications.

14 THE COURT: Go ahead.

15 DIRECT EXAMINATION

16 BY MR. HOGAN:

17 Q. Good afternoon, Dr. Rabinow.

18 A. Good afternoon.

19 Q. Have you been retained as an expert in this
20 case?

21 A. I have.

22 Q. In what area do you consider yourself to be an
23 expert?

24 A. In the pharmaceutical formulations,
25 particularly fluids, sterile fluids in

1 particular.

2 Q. Can you please provide the Court a summary of
3 your educational background after high school?

4 A. I went to Cornell University where I received a
5 bachelor's degree in chemistry then went to the
6 University of Chicago where I got a masters and
7 a PhD in physical organic chemistry.

8 Q. Do you have any training after your PhD?

9 A. Yes, I do. I did a post-doc in the electric
10 industry, and then I decided that I wanted to
11 get closer to human health, medical diagnosis,
12 this kind of thing. So I did an NIH
13 post-doctoral fellowship in clinical chemistry
14 at what was then Michael Reese Hospital in
15 Chicago.

16 Q. Can you briefly tell me what is clinical
17 chemistry?

18 A. Clinical chemistry is the application of
19 chemistry to the diagnosis and treatment of
20 human health from the standpoint of chemical
21 applications.

22 Q. Can you please describe your professional
23 background after your post-doctoral work?

24 A. So after I did my post-doctorate, my clinical
25 chemistry post-doc, I became director of

1 chemistry at an inner city Chicago hospital
2 where I ran the labs, interacted with the
3 medical faculty, developed new tests, attended
4 grand rounds. And that lasted for maybe a year
5 or so. Then I went to Baxter Healthcare.

6 Q. And can you briefly describe your experience
7 and your responsibilities while at Baxter
8 Healthcare?

9 A. So I started as a bench level chemist,
10 developed assays and resolved some critical
11 problems they were having with their major
12 product lines that resulted in a number of
13 successive promotions to the point where I
14 became director of chemistry at Baxter, which
15 involved being heads of the analytical labs,
16 the synthetic chemistry labs, material science
17 which dealt with plastics, and even toxicology
18 for a while there.

19 Q. During your experience and your time with
20 Baxter did you work on pharmaceutical
21 formulation projects?

22 A. Certainly, that was a critical aspect of it.

23 Q. Can you describe some of that work you did at
24 Baxter?

25 A. So shortly after I arrived there, there were

1 major problems with an intravenous amino acid
2 injection product that they had launched. They
3 were finding all sorts of colors, particulates,
4 that were forming over time and I was given the
5 mandate to fix it. So quickly had to figure
6 out what was going on and reformulate the
7 product, work with manufacturing to change some
8 of the critical manufacturing parameters to
9 eliminate the problem.

10 Q. Did your experience at Baxter commonly include
11 batches of work where as degradation of drug
12 products and why and how that happened?

13 A. Yeah, that was a critical factor of it. So
14 typically one would find with any problem that
15 typically there would be some kind of
16 degradation, either chemical degradation,
17 formation of particulates, whatever, and then
18 the issue would be what is the reaction and how
19 fast is it occurring. I would apply my
20 background in chemistry to understand the
21 mechanism of the reaction and the kinetics,
22 which is how fast does the reaction occur. So
23 that enabled me to solve a lot of problems.

24 THE COURT: Excuse me. Can you turn
25 counsel's microphone up?

1 MR. HOGAN: I think, is that better.

2 THE COURT: I think the court report
3 was having trouble.

4 BY MR. HOGAN:

5 Q. Dr. Rabinow, could you give me an idea how many
6 pharmaceutical formulations you worked on
7 during your experience at Baxter?

8 A. So adding up everything that I worked on
9 individually as well as a part of the team as
10 well as overseeing a large part of the effort
11 it was in excess of 50 fluid, sterile fluid
12 injectable products as well as Kaplan, major
13 problem with synthroid formulations with the
14 19th most prescribed drug at that time.

15 Q. Can you give me an idea how many products or
16 projects you worked on at Baxter that was
17 liquid formulations?

18 A. It was in excess of 50, maybe 55, something
19 like that.

20 Q. And you were directly involved in that work; is
21 that right?

22 A. I was directly involved in doing the work, in
23 supervising chemists who analyzing and
24 formulating the products. I sat on what was
25 called the exredating review committee, which

1 means that any time a product had advanced to
2 the point that it was about to be submitted to
3 FDA, we needed to recommend the dating so we
4 would evaluate all of the data and recommend
5 the dating for it.

6 Q. Okay. I want to switch gears now. Do you
7 belong to any professional associations?

8 A. Right now just the American Chemical Society.

9 Q. How about before that?

10 A. Before that with Baxter it was advantageous to
11 belong the Parenteral Drug Association, the
12 PDA. AAMI, A-A-M-I, the American Association
13 for Medical Instrumentation, HEMA, Health
14 Industrial Manufacturer's Association. There
15 may have been others.

16 Q. Have you won any awards during your career?

17 A. There's about a dozen awards I won for solving
18 problems and developing innovative formulations
19 at Baxter. Perhaps the most prestigious was
20 when they awarded me the title of Baxter
21 distinguished scientist, which is a title that
22 only maybe 12 people throughout the
23 50,000-person organization receive.

24 Q. Do you have any journal publications?

25 A. I have about 43 journal publications.

1 Q. Generally to what subject matter do those
2 publications relate to?

3 A. Injectable formulations, narrow suspension,
4 liquid formulations, overviews, for example, in
5 Remington's, Pharmaceutical Sciences, issues
6 of absorption of protein drugs onto plastic
7 material surfaces. But generally formulations
8 and the problems experienced in formulation.

9 Q. Are you a named inventor on any patents?

10 A. I've got about 16 patents to my credit.

11 Q. What subject matter do these patents relate to
12 generally?

13 A. Formulations, either liquids, and particularly
14 nano suspensions, new novel means of
15 sterilizing liquid drugs, things of that
16 nature.

17 Q. Have you been invited to present papers to any
18 professional organizations during your career?

19 A. I'm sorry.

20 Q. Let me try it again. Have you been invited to
21 present papers to any organizations during your
22 career?

23 A. Perhaps a couple dozen.

24 Q. Couple dozen. Okay how long were you at
25 Baxter?

1 A. Over 39 years.

2 Q. Have you done consulting work for the
3 pharmaceutical industry?

4 A. I did. After I left Baxter in 2016 I joined a
5 company called by BioPhia Consulting where we
6 consulted directly to the pharmaceutical
7 industry and actually back at Baxter for about
8 a year and then I started my own company where
9 I hired myself out as both an expert witness
10 and continued consulting for the pharmaceutical
11 companies.

12 Q. In your binder, Dr. Rabinow, could you please
13 turn to DTX 1010?

14 A. 1010.

15 THE COURT: Before these exhibits,
16 any issue with any of these?

17 MR. KONG: They identified three
18 exhibits. We have no objection.

19 THE COURT: Three, there's a lot more
20 in my binder. Which ones do you want to use?

21 MR. HOGAN: Your Honor, the binder is
22 all the expert reports by Alkem's experts and
23 their CVs and any attachments to the reports.

24 THE COURT: Which one are the
25 exhibits?

1 MR. HOGAN: The exhibit I'm going to
2 show now is DTX 1010. And the exhibits for
3 this witness are not all in that binder.
4 That's just the experts.

5 THE COURT: I know. 1010. Which
6 three are you going to use? 1010.

7 MR. HOGAN: We're going to use 1010,
8 that's Dr. Rabinow's CV.

9 THE COURT: Right.

10 MR. HOGAN: We're going to look at
11 1002, which is the '621 patent, I believe
12 that's PTX 2.

13 THE COURT: 10.

14 MR. HOGAN: 1002.

15 THE COURT: And what else?

16 MR. HOGAN: We're going to look at
17 DTX 1144.

18 THE COURT: Are you moving for the
19 admission of the exhibits?

20 MR. HOGAN: Yes, Your Honor.

21 THE COURT: Any objection?

22 MR. KONG: Only to the extent that
23 one of the exhibits has already been marked.
24 So can we keep the consistent numbering so the
25 record is not a mess? PTX 2, I believe is the

1 second exhibit.

2 THE COURT: I'm going to let the two
3 of you figure that out and work with Sierra on
4 that. I agree we should have one exhibit so
5 there's not two exhibits. Aside from that, no
6 objection?

7 MR. KONG: No, Your Honor.

8 THE COURT: They're admitted.

9 Which one are we on now?

10 (Thereupon, Exhibit Numbers PTX 2, DTX
11 1002, DTX 1010, and DTX 1144 were admitted.)

12 MR. HOGAN: We are on DTX 1010, Your
13 Honor.

14 BY MR. HOGAN:

15 Q. Dr. Rabinow, do you have 1010 in front of you?

16 A. Yes.

17 Q. What is that?

18 A. It's my CV.

19 THE COURT: It's in the binder. I'm
20 confused. You handed up a binder DTX 1010 and
21 the CV is in the binder. I just want to make
22 sure I'm following what you're doing, but now
23 you just handed up another 1010.

24 MR. HOGAN: We're marking this as an
25 exhibit, it's his CV.

1 MR. HOGAN: I intend to go no
2 further. I just wanted to clarify it didn't
3 matter for his opinions.

4 THE COURT: I just wanted to know
5 what level to pay attention.

6 MR. HOGAN: Understood, Your Honor.

7 BY MR. HOGAN:

8 Q. Let's shift gears and go to DDX 002.
9 Dr. Rabinow, did you prepare some slides on
10 several backgrounds for your testimony today?

11 A. Yes.

12 Q. Can you walk us through at a high level the
13 information that's depicted on DDX 002?

14 A. There were two different major types of
15 excipients insofar as they affect pH. You have
16 strong acids and bases such as hydrochloric
17 acid and sodium hydroxide, they are used to
18 adjust pH, they change the value. Buffers, on
19 the other hand, comprise weak acids and bases
20 and they are used to maintain the pH.

21 Q. What can you tell me about how pH works
22 generally in liquid formulations?

23 A. So in water solutions the pH refers to a
24 measure of the proton concentration and it
25 varies over astronomic orders of magnitude, 10

1 to the 14th. Because people don't like to talk
2 in terms of exponents they use the logarithm of
3 that. So instead of referring to 10 to the
4 14th levels of protons they refer to 14. So
5 the pH scale typically ranges from 0 to 14 with
6 0 being the most acidic and 14 being the most
7 basic.

8 THE COURT: Hold on a second. Can
9 you read back his answer, please.

10 THE REPORTER: So in water solutions
11 the pH refers to a measure of the proton
12 concentration and it varies over astronomic
13 orders of magnitude, 10 to the 14th. Because
14 people don't like to talk in terms of exponents
15 they use the logarithm of that. Instead of
16 referring to 10 to the 14th levels of protons
17 they refer to 14. So the pH scale typically
18 ranges from 0 to 14 with 0 being the most
19 acidic and 14 being the most basic.

20 THE COURT: And you were going to
21 move on to your next question. You actually
22 expect that I would understand that answer?
23 Don't you want to break it down into terms that
24 a judge, a lawyer, would understand?

25 MR. HOGAN: I can ask another

1 question, Your Honor.

2 THE COURT: So why don't you ask him
3 another question or you can move on and I won't
4 understand his answer, it's up to you.

5 BY MR. HOGAN:

6 Q. Dr. Rabinow, so the pH scale is exponential; is
7 that right?

8 A. Yes.

9 Q. And it's done 0 to 14 to make it more easy to
10 handle for practitioners; right?

11 THE COURT: What is 0 to 14, what's
12 the scale?

13 BY MR. HOGAN:

14 Q. What does a pH of 0 represent?

15 A. pH 0 represents a concentration of ten to the
16 minus 0 moles of protons.

17 Q. Is that basic or acidic?

18 A. It's highly acidic.

19 Q. pH 14 is basic or acidic?

20 A. Highly basic.

21 Q. What's the middle of the range?

22 A. 7.

23 THE COURT: I'm asking you,
24 Mr. Hogan, why are you asking these questions
25 reconnect me to the issue that you called this

1 witness for. Explain it.

2 MR. HOGAN: Yes, sir. One of the
3 things I'm going to ask Dr. Rabinow to explain
4 is about pH as it relates to formulations in
5 this case, the stability formulation in the
6 Epaned ready to use formulation, pH -- he's
7 going to explain how pH was relevant to the
8 prior art and how it impacts the stability of
9 the molecule enalapril and I was trying to do a
10 little background to make pH more
11 understandable which obviously didn't go as I'd
12 hoped.

13 THE COURT: That's why I like bench
14 trials. I will raise my hand and say I'm not
15 following. Why are we going into prior art,
16 remind me of that here? We're talking about
17 noninfringement; right?

18 MR. HOGAN: It's more of a technology
19 background really was the intent.

20 THE COURT: What does prior art have
21 to do with your noninfringement?

22 MR. HOGAN: Nothing, Your Honor, I
23 misspoke, I meant technology background.

24 THE COURT: So you're laying
25 technology background to get to his opinion as

1 to why your client doesn't infringe; right?

2 MR. HOGAN: Yes.

3 THE COURT: Go ahead.

4 BY MR. HOGAN:

5 Q. DDX 003 is on the screen. Can you walk the
6 Court through this slide, this demonstrative,
7 with what it would tell and why it's important
8 to your opinions?

9 A. Right. So this is a slide that actually
10 appeared in the patents. The publication was
11 referenced in the patents and it appeared in
12 2001 and it was a clear demonstration of the
13 effect of pH upon the stability of enalapril
14 maleate. So if you look there you will see and
15 what we're plotting here is the lot of the
16 remaining concentration of the drug with the
17 highest point in the northwest corner being the
18 highest drug and as you proceed downward in the
19 southeast direction things become progressively
20 more degraded.

21 Q. Dr. Rabinow, what does this chart show relative
22 to your opinions?

23 A. So it shows the effect of pH on the stability
24 of enalapril maleate.

25 Q. What does this tell you about the stability of

1 enalapril maleate?

2 A. This tells us that line D corresponding to pH
3 3.4 is the most stable.

4 Q. I want to focus on the '621 patent first.
5 Could I have PTX 2. This is the '621 patent,
6 Doctor; right?

7 A. Correct.

8 Q. And you've read it; right?

9 A. Yes.

10 Q. You considered this document as part of your
11 work in this case, didn't you?

12 A. Yes.

13 Q. Okay. You were in the courtroom this morning,
14 were you not?

15 A. I was.

16 Q. And you're aware that Azurity is asserting
17 claims 4, 7, 17, and 18 against Alkem in this
18 case?

19 A. I'm sorry, repeat that question.

20 Q. You're aware that Azurity is asserting claims
21 4, 7, 17, and 18 in this case; correct?

22 A. Yes, that's correct. Yes.

23 Q. And you understand the claims?

24 THE COURT: Are we needing something?

25 THE CLERK: I'm trying to find the

1 Q. Hello, sir. How are you?

2 A. Good.

3 Q. Nice to see you again.

4 A. You too.

5 Q. On direct testimony, you offered no opinion
6 regarding noninfringement of the '482 patent;
7 is that correct?

8 A. That's correct.

9 MR. KONG: Your Honor, give me one
10 moment. I was expecting testimony on that
11 subject. I'll rearrange my outline really
12 fast.

13 THE COURT: Take your time.

14 And I can ask Mr. Hogan, so how does it
15 affect the case? I heard the same thing. He
16 didn't offer any opinions on '482.

17 MR. HOGAN: That's right, Your Honor.

18 THE COURT: How does that affect your
19 case? What are you saying? You're not
20 offering evidence?

21 MR. HOGAN: No opinions from this
22 witness on infringement for '482, Your Honor.
23 That's right.

24 THE COURT: So are you conceding? Do
25 you have -- what is your case that you don't

1 infringe '482?

2 MR. HOGAN: So we're not conceding
3 infringement, Your Honor. As you know, that's
4 claims we're going to prove, and we'd like the
5 chance to brief it based on our contention that
6 there's disclaimer based on --

7 THE COURT: Say the last part.

8 MR. HOGAN: We'd like to reserve the
9 right to brief this --

10 THE COURT: We're going to have
11 briefing and discussion. You don't waive
12 anything. I'm wondering why they put on a case
13 about infringement on '482 and you don't have
14 an expert, so explain. Where is this going?

15 MR. HOGAN: We're not, Your Honor. I
16 don't want -- it is our decision that that's
17 how we want the witness to testify, just to the
18 '621.

19 THE COURT: But you're not conceding.
20 Let him answer. He's doing fine.

21 Are you saying that they can't meet their
22 burden? Do you have a case on this? Tell me
23 what's going on.

24 MR. HOGAN: I think we do.

25 THE COURT: What's the evidence?

1 MR. HOGAN: It's not based on expert
2 testimony. It's based on the intrinsic record
3 of the patent.

4 THE COURT: Okay. And you're going
5 to explain that later. That's all I wanted to
6 know. We're not going to offer expert
7 testimony, but there's documents that we're
8 going to be able to rely upon, and we're going
9 to explain to you how they connect at a later
10 point in this case or in briefing that are
11 going to show we don't infringe the '482. Is
12 that what you're trying to tell me?

13 MR. HOGAN: We're going to try do to
14 do that, Your Honor.

15 THE COURT: You're going to try to do
16 that. All right. Go ahead. Cross-examine.

17 BY MR. KONG:

18 Q. Alkem performed a compatibility study on the
19 excipients in its ANDA product; is that right?

20 A. I believe they did.

21 Q. And the excipients in the ANDA product include
22 parabens and sugar alcohols; right?

23 A. I don't recall.

24 Q. You don't recall. We can move on then.

25 To your knowledge, has Alkem ever

1 do you agree that it's dissociated?

2 THE WITNESS: It is dissociated but
3 it was dissociated before you added it into the
4 solution.

5 BY MR. KONG:

6 Q. Let's turn to DTX 1144, Figure 1, which is on
7 page 898. This is an exhibit the witness
8 testified about on direct.

9 THE COURT: What was the document?

10 MR. KONG: DTX 1144.

11 THE WITNESS: Okay. Thank you.

12 MR. KONG: This is the reference of
13 the Al-Omari paper that you discussed in your
14 direct; is that right?

15 We're on page 898 Figure 1, please. And
16 it was Figure 1, if we could get to 898,
17 please. There it is.

18 So it was Figure 1 that you testified on
19 direct provides clear demonstration of the
20 effect of pH on enalapril; is that correct?

21 THE WITNESS: Yes.

22 BY MR. KONG:

23 Q. Let's look at Figure 1. In the X axis I see
24 time measured in hours; right?

25 A. Yes.

1 Q. And it goes from 0 all the way to 140; is that
2 right?

3 A. 140 hours, yes.

4 Q. And in the Y axis, it says the enalapril
5 maleate remaining?

6 A. Yes.

7 Q. In the Y axis we see three ones and four twos?

8 A. Yes.

9 Q. Visually there's no distinction between the
10 ones in the Y axis?

11 A. That is clearly a misprint. They made a
12 mistake in the demonstrative.

13 Q. So we agree the table has a mistake in it?

14 A. Yes.

15 Q. Can you tell me with any certainty what percent
16 enalapril maleate remains for the sample A at,
17 say, 0 hours?

18 THE COURT: Hold that thought for a
19 second. Could you just tell me DTX 144 is --
20 what are we looking at?

21 MR. KONG: 1144.

22 THE COURT: I have it. I want to
23 know what it's part of.

24 MR. KONG: On direct, Dr. Rabinow
25 testified that this was the figure that he

1 relied upon for his testimony that there was a
2 clear demonstration of the effect of pH on
3 enalapril.

4 THE COURT: So this is, what, a
5 journal article?

6 MR. KONG: That's correct.

7 THE COURT: Got it. Thanks. Go
8 ahead.

9 THE WITNESS: I see that the numbers
10 vary from on the log scale, from two down to
11 one, so I would say that there is at least a
12 tenfold loss of potency, perhaps more.

13 BY MR. KONG:

14 Q. Sir, that's not my question.

15 THE COURT: Let him finish. Maybe he
16 was getting to your answer.

17 THE WITNESS: From that standpoint,
18 that's a significant loss, even though I can't
19 give you a precise answer as to exactly how
20 much was lost.

21 BY MR. KONG:

22 Q. So you agree with me then that you can't give a
23 precise answer regarding how much loss is
24 demonstrated by this Figure 1?

25 A. It maybe in the body of the paper, but I don't

1 recall at this point. That's correct.

2 Q. Sir, your testimony was on the table; right?

3 In this table can you tell me the precise
4 amount of pH that was lost over time from any
5 of the samples?

6 A. Not by looking at this table directly, but I
7 can estimate that at least it was a tenfold
8 loss.

9 Q. And your estimation is based on the change from
10 2 to 1?

11 A. Yes.

12 Q. Is that right?

13 A. Right.

14 Q. What about the change from 2 to 2?

15 A. Well, what's going on there is that these
16 numbers probably refer to something like 2.1,
17 2.2, 2.3, 2.4 something like that.

18 Q. That's my point. We don't know what they refer
19 to.

20 A. I don't know, but I just know from other people
21 who are making log graphs. That's what they
22 would put in there.

23 Q. But you're using an assumption and applying it
24 to the paper; right?

25 A. Al-Omari isn't the only paper that says pH 3.1

1 THE COURT: Give him a second to get
2 there.

3 THE WITNESS: Okay.

4 BY MR. KONG:

5 Q. And do you see that you referred to the U.S.
6 Patent 9,669,008 in your report?

7 A. Yes.

8 Q. And you're aware that this patent 9,669,008
9 shares the same specification as the patents
10 asserted in this case; right?

11 A. I don't recall.

12 Q. You don't recall?

13 A. No.

14 Q. Okay.

15 THE COURT: Are you going to impeach
16 him with a deposition?

17 MR. KONG: No, I just want to get
18 this deposition into evidence.

19 THE COURT: Maybe Mr. Hogan will
20 agree with the premise of your question.

21 MR. KONG: I want to put the '008
22 into evidence. And we agree that it shares the
23 same specification.

24 THE COURT: Do you agree that it
25 shares the same specification?

1 MR. HOGAN: So agreed.

2 THE COURT: So stipulated.

3 MR. KONG: So I don't need the move
4 the exhibit in, and I'm done with this witness.

5 THE COURT: Any redirect, Mr. Hogan?

6 MR. HOGAN: Briefly, Your Honor.

7 THE COURT: Sure.

8 The lawyers always think the judges are
9 impatient about redirect, every time. I
10 probably did the same thing. Briefly, Your
11 Honor. Just one question. If you're efficient
12 and it's proper redirect, it doesn't have to be
13 brief. Go ahead. Ask him what you want to ask
14 him.

15 REDIRECT EXAMINATION

16 BY MR. HOGAN:

17 Q. Dr. Rabinow, Mr. Kong asked you some questions
18 a new minutes ago about the Al-Omari reference
19 in that table. Do you remember that?

20 A. Yes.

21 Q. And that comes out of a publication it's in the
22 Journal of Pharmaceutical and Biomedical
23 Analysis; right?

24 A. Yes.

25 Q. In your opinion, is that a reliable journal?

1 43103. Do you recognize Exhibit 7,
2 Mr. Pradhan?

3 A. Yes.

4 Q. And what is Exhibit 7?

5 A. This is a lab notebook.

6 Q. Do you see -- if you look in the box on page
7 43010 do you see where the name of the product
8 says enalapril maleate oral solution 1
9 milligram per milliliter?

10 A. The lab notebook is enalapril maleate oral
11 solutions 1 milligram per milliliter.

12 Q. And that's the ANDA product; correct?

13 A. Yes.

14 Q. And looking at the box what is the day month
15 and year that this lab notebook was issued?

16 A. The issue date is 11th of September that is
17 092017.

18 THE COURT: Okay. That's it?

19 MR. KONG: That's it.

20 THE COURT: Okay. I don't think it's
21 going to be productive to start with the
22 invalidity case now. So let's call it a day.
23 Tomorrow it will be -- so we're going to start
24 with defense tomorrow; is that right? You're
25 going to call the witness first?

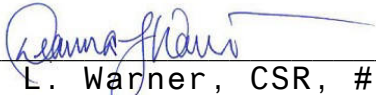
C E R T I F I C A T E

STATE OF DELAWARE)
) ss:
COUNTY OF NEW CASTLE)

I, Deanna L. Warner, a Certified
Shorthand Reporter, do hereby certify that as
such Reporter, I was present at and reported in
Stenotype shorthand the above and foregoing
proceedings in Case Number 19-2100-MSG, *AZURITY
PHARMACEUTICALS, INC. Vs. ALKEM LABORATORIES,
LTD.*, heard on August 16, 2022, before the
Honorable Mitchell Goldberg, U.S.S.J.

I further certify that a transcript of
my shorthand notes was typed and that the
foregoing transcript, consisting of 236
typewritten pages, is a true copy of said **BENCH
TRIAL.**

SIGNED, OFFICIALLY SEALED, and FILED
with the Clerk of the District Court, NEW
CASTLE County, Delaware, this 26th day of
August, 2022.


Deanna L. Warner, CSR, #1687

IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC.,)
)
-----Plaintiff,)
) Case No.
vs.) 19-2100-MSG
)
ALKEM LABORATORIES LTD.,)
) Volume II
-----Defendant.)

TRANSCRIPT OF BENCH TRIAL

BENCH TRIAL had before the Honorable
Mitchell S. Goldberg, U.S.D.C.J., in Courtroom
4B on the 17th of August, 2022.

APPEARANCES

MORRIS NICHOLS ARSHT & TUNNELL LLP
BY: MEGAN DELLINGER, ESQ.

-and-

WILSON SONSINI GOODRICH & ROSATI
BY: T.O. KONG, ESQ.
WENDY DEVINE, ESQ.
TINA HANSON, ESQ.
EVAN SUMNER, ESQ.
JODY KAROL, ESQ.
JESSICA RAMSEY, ESQ.

Counsel for Plaintiff

1 THE COURT: So you're going to call
2 Dr. Constantinides.

3 MR. KRATZ: Your Honor, before we do
4 that, we're going to formally put the
5 depositions in the record that we had and a few
6 exhibits that go with it. We'll take care of
7 that and then proceed, if I may.

8 THE COURT: Go ahead.

9 MR. KRATZ: So what I have is the
10 deposition clip reports, and I have the video,
11 if Your Honor cares to watch the witnesses. I
12 have one copy of the video. We can make more.

13 THE CLERK: We can make more. I want
14 to make sure Sierra has it.

15 MR. KRATZ: I'm the same way. Those
16 are the depositions. It's Mosher, who's one of
17 the inventors, and Miles, who's the other named
18 inventor.

19 MR. KONG: Your Honor, before you
20 watch the video of Mr. Miles testify, for Your
21 Honor's background, he's hearing impaired.
22 When he was being deposed, he was reading the
23 realtime so he could get the question, and
24 attorneys had to look at documents, just for
25 your own background.

1 MR. SUMNER: Your Honor, we have an
2 exhibit we're going to enter with Dr. Mosher.

3 THE COURT: Let him finish with the
4 exhibits.

5 MR. KRATZ: I apologize for this
6 being needlessly complex, but we will correct
7 it between the parties as we discussed, but
8 there are some duplicative exhibits, but we had
9 given a list of the exhibits we intended to
10 introduce through these witnesses. It's all
11 done by agreement, so I'll read the list of
12 what we've got to enter, but they're going to
13 have different designation numbers in different
14 spots. I think we agreed on what number to
15 ultimately use for trial and then the
16 transcript. My hope is we can clean all that
17 up by agreement at some point, but for now --

18 THE COURT: You can do that, that's
19 fine, and you probably thought of this, but
20 when we're done and the record here is
21 complete, you get together and then you submit
22 by agreement, what you've gone over by
23 agreement, these are -- we've reviewed with
24 your courtroom deputy, Ms. Steigner, and the
25 exhibits, and here is one pristine copy without

1 duplication.

2 MR. KRATZ: It's extra paper, but for
3 now what we're going to do is introduce through
4 the witness Miles DTX 1016 and 1017, and
5 through Mr. Mosher -- Dr. Mosher, I'm sorry,
6 DTX 1032, 1033, 1034, 1036, 1039, 1040, and
7 1041.

8 THE COURT: Okay. Without objection?

9 MR. KRATZ: It's my understanding.

10 MR. KONG: Mr. Sumner is going to
11 address this.

12 MR. SUMNER: No objection, Your
13 Honor.

14 THE COURT: Again, I'm really going
15 to when the time is right --

16 MR. KRATZ: We'll take the time.
17 We'll get it right.

18 THE COURT: I want to say again
19 that's a big stack of documents, and I'm not
20 going to look favorably on arguments raised
21 through page 49 of a document that has had no
22 reference in this courtroom or really hasn't
23 been raised before. I'm not going to allow
24 that, just so everyone -- I'm not saying you're
25 going to do it, but I've seen it done in patent

1 cases where a big stack of documents is
2 introduced and then an argument is raised in
3 the post briefing that I never heard of. Well,
4 it's in evidence Judge, look, page 49, we want
5 to make this argument. I'm not going to
6 consider that.

7 MR. KRATZ: We understand that's
8 fair. The transcript that we've handed in, it
9 refers to every one of the documents.

10 THE COURT: Okay.

11 MR. KRATZ: But we understand.

12 THE COURT: All right. So those are
13 admitted.

14 (Thereupon, Exhibit Numbers DTX 1016,
15 1017, 1032, 1033, 1034, 1036, 1039, 1040, and
16 1041 were admitted.)

17 MR. KONG: And Your Honor, plaintiffs
18 have one exhibit to introduce with Dr. Mosher.
19 And that's PTX 41.

20 THE COURT: DTX.

21 MR. SUMNER: PTX 41.

22 THE COURT: It's admitted.

23 (Thereupon, Exhibit PTX 41 was
24 admitted.)

25 THE COURT: All right, thanks. We're

1 ready for the witness?

2 MR. HOGAN: Yes, Your Honor.

3 THE COURT: Call your next witness.

4 MR. HOGAN: Defendant calls

5 Dr. Panayiotis Constantinides.

6 THE CLERK: Please state and spell
7 your name for the record.

8 THE CLERK: Panayiotis, first name.
9 Middle initial is P. The first name is
10 P-A-N-A-Y-I-O-T-I-S P, and the last name is
11 C-O-N-S-T-A-N-T-I-N-I-D-E-S.

12 THE CLERK: Do you affirm that the
13 testimony you give to the court will be the
14 truth, the whole truth, and nothing but the
15 truth you do so affirm?

16 THE WITNESS: I do.

17 THE COURT: Do you want to talk about
18 exhibits?

19 MR. HOGAN: Yes, Your Honor. We have
20 some demonstratives to hand up and we have some
21 actual DTX exhibits to hand up.

22 THE COURT: All right. Let's do the
23 exhibits first.

24 MR. HOGAN: Mr. Kong has a copy.

25 THE COURT: All right. Which of

1 these, are some of these already in evidence?

2 MR. HOGAN: I do not believe so, Your
3 Honor.

4 THE COURT: Which ones do you want to
5 move in?

6 MR. HOGAN: All of them.

7 THE COURT: Say it.

8 MR. HOGAN: Yes, sir. DTX 1000, DTX
9 1002, DTX 1005, DTX 1067, DTX 1073, DTX 1074,
10 DTX 1077, DTX 1078, DTX 1081, DTX 1082, DTX
11 1083, DTX 1094, DTX 1109, DTX 1118.

12 MR. KONG: No objection.

13 THE COURT: They're admitted.

14 (Thereupon, DTX Numbers 1000, 1002
15 1005, 1067, 1073, 1074, 1077, 1078, 1081, 1082,
16 1083, 1094, 1109, and 1118 were admitted.)

17 THE COURT: Okay. And then you have
18 a demonstrative for this witness?

19 MR. HOGAN: Yes, Your Honor.

20 THE COURT: Pass that up, please.

21 All right. The witness is offered as an expert
22 in what field?

23 MR. HOGAN: In pharmaceutical
24 formulation.

25 THE WITNESS: In pharmaceutical

1 formulation.

2 THE COURT: I'm asking the lawyer.

3 MR. HOGAN: Pharmaceutical
4 formulation.

5 THE COURT: What does that mean?

6 MR. HOGAN: The witness can explain
7 or I can do that, sir.

8 THE COURT: I'm asking you.

9 MR. HOGAN: That is the preparation
10 of pharmaceutical dosage forms, including their
11 design and development, and the contents of
12 those dosage forms, be it liquid or gels or
13 oral liquid, as is the subject matter of this
14 case.

15 THE COURT: To offer opinions in what
16 area?

17 MR. HOGAN: He's offering opinion on
18 areas of obviousness. He's going to offer
19 opinions and give some background about
20 formulation development. He will offer
21 opinions on invalidity based on Section 112 of
22 the patent statute and the subsections
23 indefiniteness, written description, and
24 enablement. The latter defenses, Your Honor,
25 under Section 112, do not apply to all the

1 asserted claims but certain specific claims,
2 which we're going to get into.

3 THE COURT: And you're not going to
4 elicit testimony unless it's needed on issues
5 that are purely legal; right?

6 MR. HOGAN: Yes, sir. I'm cognizant
7 of that. I will do my best.

8 THE COURT: And I know there's issues
9 that overlap. Does Plaintiff have an objection
10 to the proffer that you just heard?

11 MR. KONG: No objection.

12 THE COURT: All right. So he's
13 accepted as an expert. You can lead him
14 through his qualifications or not. It's up to
15 you. Go ahead.

16 MR. HOGAN: And, Your Honor, I
17 appreciate the time constraints, and we'll be
18 brief with the background, but I think it's
19 relevant for Your Honor.

20 THE COURT: Go ahead.

21 DIRECT EXAMINATION

22 BY MR. HOGAN:

23 Q. Good morning, Dr. Constantinides.

24 A. Good morning.

25 Q. I believe you prepared a slide show to help you

1 Brown University, and post-doctorate training
2 in pharmacology at Yale University. Looking
3 back with educational background in chemistry
4 biochemistry and pharmacology served me very
5 well in my industrial career.

6 Q. Can you please give us a summary of your
7 professional experience after you completed
8 your post-doctoral work.

9 A. Yes. After my post-doctoral, I joined a small
10 company in Knoxville, Tennessee, by the name
11 LipoGen, using the liposome-based technologies
12 for diagnostic and therapeutic applications. I
13 was working on the therapeutic applications of
14 the technology, initially as a scientist and
15 later as a manager of the therapeutics division
16 of the company.

17 Q. Doctor, let me ask a quick question. We can
18 maybe expedite this. In your experience after
19 post-doctoral training in the pharmaceutical
20 industry, did you work on developing
21 formulations that included liquid formulations?

22 A. Yes.

23 Q. At several companies; correct?

24 A. Yes -- yes.

25 Q. Okay. Can you give me the names of some other

1 companies you worked at?

2 A. At LipoGen I developed a liposome mixture which
3 is a mixture of phospholipids, in this case
4 with ethanol liquid formulation which can be
5 used both for oral and for rectal
6 administration.

7 Q. Sir, can you -- can you give me the companies
8 you worked at, not necessarily all the
9 formulations you did.

10 A. Lipogen was the company.

11 Q. What was the next one?

12 A. Then I joined, after Lipogen, SmithKline
13 Beecham Pharmaceuticals as senior investigator.
14 And there, my primary responsibility to deliver
15 orally peptides and proteins, a very
16 challenging undertaking, using oral liquids in
17 this case and more specifically any
18 macroemulsion-type formulations, water and oil,
19 filling to a capsule.

20 Q. Where did you work after SmithKline Beecham?

21 A. I joined Abbott Laboratories. The intent of my
22 role there, I was section head of a small group
23 of scientists focused on the development of
24 oral liquid formulations. That includes
25 suspensions, solutions which can be filled into

1 a bottle or vial or fill into a capsule, heart
2 of a capsule. At that time also I was project
3 leader on a generic version of Novartis Neoral,
4 which is the cyclosporine oral formulation
5 which is an oral liquid, in this case
6 semi-solid, which makes at room temperature is
7 semi-solid but 37 degrees body temperature is
8 converted to liquid, and that project was
9 approved in 2000, May of 2000, by the name
10 GENGRAF.

11 Q. How long did you work in the pharmaceutical
12 industry? How many years?

13 A. I will say 35 years to this day.

14 Q. Do you belong to any professional associations?

15 A. Can you please repeat the question.

16 Q. Yes. Do you belong to any professional
17 associations?

18 A. Yes. I do belong to American Chemical Society,
19 Controlled Release Society and the American
20 Association of Pharmaceutical Scientists.

21 Q. Have you won any awards during your career?

22 A. Yes. I have received awards in my career. I
23 would say several employment awards with the
24 company I was employed by. In addition to
25 that, let me just highlight two. I was

1 A. Yes.

2 Q. Is that accurate?

3 A. Yes, it is.

4 MR. HOGAN: I'll proffer
5 Dr. Constantinides as an expert.

6 THE COURT: Already been accepted.

7 BY MR. HOGAN:

8 Q. All right. Doctor, would you please summarize
9 the opinions you've developed in this case?

10 A. Yes. The summary of my opinions is that the
11 asserted claims in the two patents, '482 and
12 '621, are invalid because they're obvious in
13 view of the prior art but, furthermore, some of
14 the claims are also invalid under
15 considerations of the 35 U.S. paragraph 112.

16 Q. Can you please summarize the process you used
17 to arrive at your conclusions in this case?

18 A. Yes. I reviewed the patents, the two key
19 patents, '482, '621, the prosecution or file
20 history. I reviewed reports, depositions by
21 the inventors. In addition to that, the prior
22 art or relevant prior art, but further to the
23 prior art, I also review and included several
24 other peer-reviewed publications in light of
25 some technical background and tutorial included

1 chemical stability. More specifically the
2 maximum stability, chemical stability for the
3 drug is around pH 3 and that's -- and above pH
4 5, the drug starts decompose. This is from
5 Allen, 1998 prior art.

6 Q. That's the prior art reference you just
7 identified; right?

8 A. Yes.

9 Q. Okay. Can you please summarize what's on slide
10 26?

11 A. Yes. This is dealing with buffers, modify and
12 maintain the pH of the buffers, again, very
13 well-known principles and methodology of a
14 POA. There are several book chapters and
15 other review articles of the matter. I just
16 highlight here an exemplary one, the book
17 chapter by de Villiers with the title "Buffers
18 and Buffering pH Adjusting Agents." So, again,
19 well known for a long time now methodologies
20 and ways how you prepare, modify and maintain
21 the pH of buffers.

22 Q. When you use the word "POA," that represents a
23 person of ordinary skill in the art?

24 A. Yes. These are very well known to a POA, yes.

25 Q. Can you briefly summarize what's on this slide,

1 Doctor?

2 A. Yes. What I summarize here is the composition
3 of the commonly used compounding vehicles in
4 one of the references that I cite here in terms
5 of their components, the buffering agents, the
6 suspension agents, making the suspensions and
7 also preservatives and other key components of
8 the preservatives in the compounding vehicles.

9 Q. The information on the left -- far left column,
10 that's the name of compounding vehicle; right?

11 A. Yes.

12 Q. How are compounding vehicles used? Why is that
13 relevant to your opinions?

14 A. How are --

15 Q. How are compounding vehicles used? Why is that
16 relevant to your opinions today?

17 A. Because those are again the commonly used
18 vehicles in reconstituting powder formulations
19 into liquid formulations.

20 Q. Okay. Next slide. Can you briefly summarize
21 what's shown on this slide?

22 A. Yes. In drug development in general, it's
23 certainly known to a formulator and to a POA
24 the so-called target product profile which
25 describes really some of the key objectives in

1 reference to the drug substance but relevant to
2 our case will also be the product related, you
3 know, attributes such as the pH, organoleptic
4 properties, the excipients used and whether or
5 not they're compendial, in other words, USP-NF.
6 That's the term used and in other marketed
7 drug products, manufacturing equipment, process
8 parameters, packaging and so on.

9 Q. Can you explain how this information is
10 relevant to your opinions in this case?

11 A. Because a POA said to develop a ready-to-use
12 oral liquid formulation of it was well aware of
13 the requirements in reference to the
14 characteristics of this product. At what pH
15 the drug may reach maximum stability? What
16 kind of dosage form in this case, oral or
17 liquid? What is the stability requirement to
18 get it to the FDA process and approval? Again,
19 that's how a POA would use the information in
20 the target product profile.

21 Q. Is this information -- is it fair to say this
22 information is representative on the
23 methodology a person of ordinary skill in the
24 art would use in developing the formulation?

25 A. Correct, yes.

1 Q. Any formulation?

2 A. Any formulation.

3 Q. Next slide, please. Can you please just
4 summarize what's shown on this slide, Doctor?

5 A. Yes. In drug development the reference again
6 to activities related to preformulation.
7 Before that there is a phase called
8 preformulation where you determine drug
9 solubility, pH dependence stability. Again,
10 that's part of the preformulation activities,
11 and then during the formulation phase, then
12 that's when you develop some prototype
13 formulations, you put in more stability and you
14 identify through the process the lead prototype
15 for further development. So that's essentially
16 what this line summarized there.

17 Q. Is it fair to say this is representing
18 information that a person of ordinary skill in
19 the art would know and develop and apply in
20 formulation?

21 A. Yes.

22 Q. I want to shift gears now and talk about your
23 obviousness opinions?

24 MR. HOGAN: Before I do that, Your
25 Honor, I want to give you a heads up where I'm

1 this inservice is later.

2 THE COURT: This is the -- we've had
3 three iterations. This is the current product.

4 MR. HOGAN: No, Your Honor. This is
5 the one with a powder that comes in two bottles
6 and we're saying this is prior art to the
7 patent in suit in this case.

8 THE COURT: This is the plaintiff's
9 product though; right?

10 MR. HOGAN: Yes. An earlier product,
11 not the product that's the subject of the
12 lawsuit.

13 THE COURT: It's a label of the prior
14 product?

15 MR. HOGAN: It is.

16 THE COURT: And this is an example of
17 prior art.

18 MR. HOGAN: It is. And you saw this
19 yesterday in Mr. Kratz's cross-examination of
20 the doctor I believe.

21 THE COURT: Okay.

22 BY MR. HOGAN:

23 Q. So looking at the contents of the bottom
24 portion of this slide, Doctor, where it says
25 the bottom paragraph, Epaned powder oral

1 solution and describes the contents, what is
2 the role of mannitol in this formulation?

3 A. The mannitol is present in dry powder
4 formulation. It's a well known bulking agent
5 or diluent.

6 Q. Would a person of ordinary skill in the art
7 want to use mannitol with a ready-to-use oral
8 solution?

9 A. No.

10 Q. Why not?

11 A. It's not needed.

12 Q. Why is it not needed?

13 A. Because again it's a bulking agent used
14 primarily for solid dosage forms.

15 Q. Is that also true of the content, component
16 silicon dioxide?

17 A. Yes. Silicon dioxide, it does improve the
18 properties of the powder but, again, commonly
19 used excipient in solid dosage form, powder
20 type formulations, not liquid solutions.

21 Q. Can you bring up DDX 031. Up on the screen in
22 the demonstratives is a presentation of prior
23 record that connects to DTX 1078. Do you
24 recognize this information in this reference,
25 Doctor?

1 A. Yes.

2 Q. What is it?

3 A. This is in Nahata prior art.

4 Q. Okay. And the title is there in the bold
5 print, stability of enalapril maleate in three
6 extemporaneously prepared oral liquids; right?

7 A. Yes.

8 Q. Okay. The call out here is the section from
9 below the -- do we have -- can I have DTX 1078.
10 Thank you. So this is DTX 1078. On the slide
11 there's the abstract section. Do you see that,
12 Doctor?

13 A. Yes, I do.

14 Q. And below the abstract section the commentary
15 begins with capital E. Do you see that?

16 A. Yes.

17 Q. This portion -- this passage here, Doctor, that
18 starts at the bottom of the first column and
19 goes to the right-hand column, how is that
20 relevant to your opinions in this case?

21 A. Okay. It says that the initial dosage is used
22 .1 milligram per kilogram but for reference,
23 but what is important to a POA is the fact
24 that it states clearly there is no liquid
25 dosage for -- it's commercially available for

1 pediatric patients in addition there are
2 limited data on the use of on enalapril in
3 extemporaneously prepared oral liquids. So
4 that would motivate the POA than indeed an
5 oral liquid formulation, a ready-to-use liquid
6 formulation, it's a medical need and certainly
7 using the prior art by having the other prior
8 art references and POA's knowledge and skills
9 you will go about developing such a
10 formulation, oral liquid formulation.

11 Q. At the bottom of the slide, the bottom right on
12 the very last line it states the name of the
13 journal. Can we blow that up, please?

14 THE COURT: Can you keep that screen
15 up there and rehighlight what you just had
16 highlighted? Is that on the first page of
17 1078.

18 MR. HOGAN: Yes, Your Honor.

19 THE COURT: Go ahead.

20 BY MR. HOGAN:

21 Q. Can we have the last line, the bottom right so
22 we can see it better. So this is the journal
23 that this article appeared in; is that right,
24 Doctor?

25 A. Yes.

1 Q. In your opinion is this journal a reliable
2 source of information to a person of ordinary
3 skill in the art?

4 A. It's a peer reviewed journal, yes.

5 Q. I want to shift now and talk about pH. Okay?
6 So if we have a person of ordinary skill in the
7 art as you describe looking to formulate a
8 ready-to-use oral formulation what kind of
9 information would they want to know to go about
10 doing that?

11 A. Again, the pH of the drug, in this case
12 enalapril maleate, is most stable, specifically
13 what is the optimal or the maximum in this case
14 pH. I'm sorry, what is the pH for the maximum
15 stability of the drug.

16 Q. Why is that information important?

17 A. Because it's an oral solution that the POSA is
18 going to develop. So oral liquid in general
19 where stability of the substances vary, but in
20 any -- in any dosage form, stability of the
21 active upon storage is a critical part of
22 formulation development.

23 Q. Okay. Can we please have DTX 1074. Okay.
24 This is another prior art reference, Doctor.
25 Do you recognize this?

1 A. Yes, I do.

2 Q. What is this?

3 A. This is the Allen 1998 peer reviewed
4 publication.

5 Q. And referencing the title, what does this
6 article deal with?

7 A. It's dealing with the stability determination
8 of a number of actives, including enalapril
9 maleate, in extemporaneously compounded oral
10 liquids.

11 Q. You see below the title there's the names of
12 the authors. Do you see those names?

13 A. Yes.

14 Q. Do you know Lloyd B. Allen, Jr.?

15 A. Do I know?.

16 Q. Do you know of Lloyd B. Allen, Jr.?

17 A. I don't know him but he's a very well respected
18 authority in the field of what he describes in
19 this publication, extemporaneously prepared
20 oral liquids.

21 Q. So we've just blown up sections of this
22 reference, this exhibit DTX 1074, I'll talk
23 about it with you Doctor. The discussion
24 section to the right here?

25 THE COURT: Are you back now on his

1 slides?

2 MR. HOGAN: Yes, Your Honor.

3 THE COURT: Okay.

4 BY MR. HOGAN:

5 Q. See the paragraph here in the discussion
6 section, Doctor?

7 A. Yes, I do.

8 Q. What information from this paragraph
9 particularly from this reference is relevant to
10 your obviousness opinions in this case?

11 A. I think the sentence there that the drug has
12 PKA -- two PKAs, the so called ionization
13 constant at 3 and 5.4 plus critical, I will
14 say, the pH of maximum stability which is
15 around three. And then subsequently it discuss
16 some references and stability that obtained
17 which is cited in his publication.

18 Q. Can we go to 33, please.

19 A. It also summarize, I'm sorry, if you go back,
20 please, yeah, it summarize stability of the
21 drug at five degrees in 25 or 90 days. In
22 other words, provide an overview of what is
23 presented in this particular publication.

24 Q. So Doctor, why is that information from this
25 reference particularly relevant to your

1 THE COURT: It's in mine, Owen. I
2 had to -- it got stuck to the previous tab.
3 It's in there. I thought it was missing as
4 well.

5 THE CLERK: You're right. Sorry.

6 THE COURT: What page are we on in
7 that exhibit?

8 MR. HOGAN: The first page.

9 THE COURT: 321.

10 MR. HOGAN: 321 to start, yes.

11 THE COURT: Okay.

12 BY MR. HOGAN:

13 Q. Doctor, do you recognize this?

14 A. Yes, I do.

15 Q. Okay. What is this?

16 A. That's the Sosnowska prior art.

17 Q. Okay.

18 MR. HOGAN: Can you blow up the top
19 left corner?

20 BY MR. HOGAN:

21 Q. Is that the date of this reference, Doctor?

22 A. Yes, 2009.

23 Q. Okay.

24 MR. HOGAN: Could we go to page 322
25 on Sosnowska.

1 BY MR. HOGAN:

2 Q. Okay. Doctor, can you tell us generally why is
3 this reference relevant to your obviousness
4 analysis in this case?

5 A. Because it deals, again, with the stability of
6 enalapril maleate which is shown in the table.
7 Can you please expand the table in that?

8 At 25 degrees ambient conditions, it
9 appears the condition is 4 degrees -- for
10 30 days up to 30 days.

11 Q. Okay.

12 MR. HOGAN: Go back to the other
13 slide and give us, please, the section under
14 formulations and preparations, that section.
15 Thank you.

16 BY MR. HOGAN:

17 Q. Doctor, in the section below, the subtitle
18 "Formulations Preparation" --

19 A. Yes.

20 Q. -- what information from this portion of this
21 reference is relevant to your obviousness
22 analysis in this case?

23 A. I will say again the maximum pH stability which
24 is around pH 3. That shows a reference, the
25 references. And, therefore, because of this

1 MR. HOGAN: This is column seven,
2 lines I think it's 56 to 57, Your Honor.

3 THE COURT: Okay.

4 MR. HOGAN: Can we go on?

5 THE COURT: Yes.

6 BY MR. HOGAN:

7 Q. Can we have slide 44, please. This is a call
8 out and this is column seven, lines 60 to 62 of
9 the '747 patent. Do you see that, Doctor?

10 A. Yes, I do.

11 Q. What is this disclosing, what does the '747
12 patent disclose concerning sweeteners?

13 A. Sweeteners and sweetening agents for taste
14 masking. The objective of this formulation is
15 to administer to young kids, infants in some
16 cases, so it's important really that you
17 improve the bitter taste which is common to
18 many drug formulations.

19 Q. When this says and calls out natural and
20 synthetic sugars, what do you take that to
21 mean?

22 A. Natural and synthetic sugars, again, those are
23 the different classes of sugars. I don't know
24 specifically.

25 Q. Can you give me example?

1 A. Sucralose, saccharin, sucralose.

2 Q. Can we go to slide 45?

3 A. Yeah.

4 Q. This is column eight, line 28 of the '747
5 patent. What does this disclose relevant to
6 your opinions, Doctor?

7 A. Specifically the sugars. And the consideration
8 as the sweetener would be sucralose, fructose,
9 xylitol, and sorbitol.

10 Q. And what's also shown on this line that's
11 disclosed in this patent?

12 A. Ora-Sweet SF, flavored syrup, and they supplied
13 it in this case part of the laboratory.

14 Q. Can we have slide DDX 46. This is column 13 of
15 the patent. This highlight, this blow up of
16 the patent, how is this relevant to your
17 opinion, Doctor?

18 A. Yes. It focus on the stability of enalapril
19 oral liquid compositions and more specifically,
20 again, it does show that the prepared enalapril
21 oral liquid compositions they have at least
22 90 percent enalapril and 5 percent or less of
23 the total impurities which includes the
24 degradants at the end of a given storage
25 period.

1 plus minus three degrees centigrade, minimum
2 12 months, at least 12 months, that's a key
3 requirement there. And then accelerated will
4 be at 25 degrees, 60 percent relative humidity,
5 that's plus minus 5 percent, that's what the H
6 stands for, for six months.

7 Q. Why is this information important to a person
8 of ordinary skill in the art as you've defined
9 it?

10 A. Because it tells the POA what type of
11 stability one needs to generate for a drug
12 product which is intended to be stored under
13 the conditions. But even so it provides
14 accelerated stability studies and the time
15 being six months which one can use to further
16 extrapolate the 12-month stability under
17 refrigerated conditions.

18 THE COURT: What exhibit is this?

19 MR. HOGAN: This is Exhibit 1109.

20 THE COURT: Give me one second,
21 please. Page 5?

22 MR. HOGAN: Yes, Your Honor.

23 THE COURT: Just so I can continue to
24 try to follow the thread of this, Mr. Kong, now
25 we have a guidance from HHS in evidence which

1 talks about long-term stability being 12 months
2 now. So how do you respond to this? What's
3 your best -- not all, your best argument to
4 respond to this?

5 MR. KONG: This document doesn't tell
6 you how to do it. It may say 12 months. It
7 doesn't tell you how to do it.

8 THE COURT: Isn't your how to do it
9 to take the powder and water and combine?

10 MR. KONG: If you're talking about
11 the kit prior art or the '747 patent, those
12 were stable for only 12 weeks.

13 THE COURT: Okay. But the current
14 invention is --

15 MR. KONG: 12 months, 12, 18, and
16 24 months.

17 THE COURT: And this is 12 months but
18 this doesn't tell you how to do it. What's the
19 it that it doesn't tell you how to do?

20 MR. KONG: So this reference that's
21 being discussed, there's no discussion about
22 enalapril in here. There's no discussion about
23 the prior art in here.

24 THE COURT: Do you agree this could
25 be considered prior art, this HHS guidance for

1 the oral liquid formulation is about .6 to 1.2,
2 are disclosed in the Epaned insert, oral Epaned
3 kit and Allen as well.

4 Q. Second element, romanette 2 here reads, "Buffer
5 comprising a mixture of citric acid, sodium
6 citrate, wherein the buffer is present at a
7 concentration of about 5 millimolar to about 20
8 millimolar of the formulation.

9 A. Let me begin by saying there are two elements
10 of the claim, the first one dealing with citric
11 acid and sodium citrate, and all three
12 references, '747, the Epaned kit and also Allen
13 disclose this again, the citric buffer. In the
14 case of there are liquids is present -- I'm
15 sorry, vehicles -- it's already present in
16 those vehicles, especially Ora-Sweet SF. In
17 reference to calculating the concentrations of
18 these liquid formulations, a POSA, as I
19 mentioned earlier during my testimony, using
20 well-known principles, so basic equilibrium,
21 and the equations described in de Villiers
22 prior art through routine application of those
23 can determine the buffer concentrations.

24 Q. And do you have a view whether or not the POSA
25 would be successful in reaching those

1 extemporaneous commercial vehicles.

2 Q. And so is your --

3 A. '747, the Epaned kit, I'm sorry.

4 Q. Okay. And so you're saying a person of
5 ordinary skill in the art would be motivated to
6 use water in this oral liquid formulation?

7 A. Water soluble drug, so water is certainly the
8 solvent for the drug in this case upon proper
9 pH adjustment using the right buffer.

10 Q. The last element of Claim 14 states, "Wherein
11 formulation maintains about 95 percent weight
12 to weight or greater of additional enalapril
13 amount at the end of the storage period of at
14 least 12 months at about 5 plus, minus 3
15 degrees C."

16 A. Yes.

17 Q. Okay. So where in the prior art is that found?

18 A. Again, in the '747 patent, Allen, they do
19 disclose that there are a range in terms of the
20 potency the, remaining potency of the drug upon
21 the investigated stability times. Now, in
22 terms of the at least 12 months, I see
23 indicated in the FDA guidance for a drug
24 product which is intended to be refrigerated,
25 the minimum requirement is at least -- or

1 minimum 12 months at 5 plus, minus 3 degrees
2 centigrade.

3 Q. Why is that important?

4 A. So that's important that the POA knows, well
5 aware of that and motivate him to pursue this
6 also with that ready-to-use liquid formulation
7 of enalapril maleate.

8 Q. Claim 15. And you're aware Claim 15 depends
9 from Claim 14; right, Doctor?

10 A. Yes.

11 Q. Okay. It reads, "Further comprising a
12 sweetener."

13 Where in the prior art does that -- is
14 that element found?

15 A. In all, again, the primary prior art '747
16 patent which state that during the
17 reconstitution of the powder formulations, a
18 sweetener is included, and we discussed earlier
19 on several sweeteners among which also is
20 sucralose. And the Epaned kit likewise
21 contains sorbitol -- includes, I'm sorry, the
22 oral SF that is used in the Epaned kit contains
23 sorbitol, sodium saccharin as sweeteners, and
24 likewise, in the Allen where Ora-Sweet and
25 Ora-Sweet SF were used. Those also contain

1 sweeteners.

2 Q. Why would a person of ordinary skill in the art
3 want to include a sweetener in an oral
4 formulation ready-to-use?

5 A. For taste purposes. After all these
6 formulations are intended for young kids. So
7 you want to have an acceptable taste in the
8 resulting oral liquid formulation.

9 Q. Claim 16. The added limitation is the
10 sweetener is sucralose. Where in the prior art
11 is this found, Doctor?

12 A. Again, specifically sucralose is listed in the
13 '747 patent in the specification among several
14 sugars was also sucralose one of them. The
15 Epaned insert, again, describes using Ora-Sweet
16 SF for reconstitution. That one also contains,
17 well, sodium saccharin, different sweetener,
18 but I will say, again, yeah, and the Allen also
19 in the compounding vehicles that they employ,
20 sweeteners are present in these compounding
21 vehicles. And then the sucralose specifically,
22 as I mentioned a minute ago, is disclosed in
23 the '747 patent.

24 Q. Okay. So next claim, Claim 18, the limitation
25 is Claim 14, wherein the formulation does not

1 contain mannitol. Doctor, why would a person
2 of ordinary skill in the art wanting to make an
3 oral liquid formulation with enalapril in it
4 not include mannitol?

5 A. Mannitol in general is a bulking agent, a
6 diluent used with powder in solid dosage forms
7 or in oral liquids. That's also based on my
8 own knowledge as well. That's why mannitol is
9 removed from an oral liquid -- ready-to-use
10 oral liquid formulation.

11 Q. Okay. Claim 22, again, depends from Claim 14
12 and the added -- the added element is wherein
13 the pH of the oral liquid formulation is about
14 3.3.

15 Doctor, why would a person of ordinary
16 skill in the art want to make an oral liquid
17 RTU formulation with that pH?

18 A. Because that is where the the drug exhibits
19 maximum stability.

20 Q. What references tell you that?

21 A. The same references that discuss the Allen
22 which discloses enalapril maleate. It
23 discussed the pH of maximum stability of -- has
24 been around 3 and above. PH 5 the drug
25 decomposes. Allen also discussed liquid

1 formulations extemporaneously with an initial
2 pH volume of around 3.9. So again that --
3 around .3, .6, .3 is something that appears in
4 the prior art references.

5 Q. Okay. And, again, a person of ordinary skill
6 in the art would be motivated to use -- to make
7 the pH of the formulation about or
8 approximately 3.3 why?

9 A. Because there's where the drug exhibits maximum
10 stability.

11 Q. Okay. Claim 23 of the '482 patent reads,
12 "hence in Claim 14 the added limitation is
13 wherein the formulation maintains about
14 95 percent weight to weight or greater of the
15 initial enalapril amount at the end of the
16 storage period of at least 18 months at about 5
17 plus or minus three degrees C."

18 Where is this found in the prior art,
19 Doctor?

20 A. Again, the '747 patent where stability of both
21 the powder compositions as well as the oral
22 liquid formulations 95 percent, at least
23 95 percent, or greater of the potency, of the
24 drug potency or drug concentration is measured
25 upon storage for at least 12 months. The POSA

1 also knows and is motivated from this
2 information in the prior art, apply also his or
3 her knowledge and expertise to optimize, to
4 further improve or extend the stability to
5 18 months or preferably two years under
6 refrigerated conditions.

7 Q. Why would a POSA be motivated to optimize
8 12 months beyond 12 months?

9 A. Because that's a requirement for the FDA.
10 Again, for any drug, when it's submitted to
11 FDA, it has to have before any approval real
12 time stability or long-term stability at the
13 designated storage temperature for 18,
14 preferably 24, months based on my own knowledge
15 and involvement as well.

16 Q. Claim 28 of the '482 patent depends on claim
17 14, the added element wherein the buffer is
18 present at a concentration between about 10
19 millimolar and about 20 millimolar in the oral
20 liquid formulation. Why would a POSA be
21 motivated to make oral liquid formulation ready
22 to use with that concentration of buffer?

23 A. As I said earlier during my testimony there are
24 several review articles guiding the POSA how to
25 better determine buffer concentrations, more

1 MR. HOGAN: Thank you, Your Honor.

2 THE COURT: Any elaboration or
3 clarification you want to ask him regarding
4 that go ahead.

5 MR. HOGAN: Thank you, Your Honor.
6 To be clear, there are some subtle differences
7 between the '482 and '621.

8 THE COURT: So ask him about that.
9 Do it.

10 BY MR. HOGAN:

11 Q. Okay, Doctor. We're going to skip down past to
12 the elements we didn't already cover.

13 A. Sure.

14 THE COURT: You know what I think
15 would be helpful before you do that so I can
16 follow what you're going to do next, let me --
17 give me a minute or two and let me scan what's
18 just been admitted. It will give me context
19 for the follow-up questions.

20 MR. HOGAN: Yes.

21 THE COURT: Go ahead.

22 BY MR. HOGAN:

23 Q. We're looking at now claim element two on the
24 bottom, the left-hand corner.

25 A. Yes.

1 Q. This says, "a buffer to maintain the pH about
2 4.5 or below." That was not in the claim we
3 talked about earlier, Doctor. What in the
4 prior art would motivate a person of ordinary
5 skill in the art to create an oral formulation
6 at pH of 4.5 or below?

7 A. Again, the pH of the reconstituted, I'm sorry,
8 the compounding vehicles as I also stated in my
9 report, the opening report, it's approximately
10 4.2. So again, this is an approximate value
11 and if indeed the purpose and basically of what
12 was disclosed in the prior art we discussed
13 earlier, Epaned, I'm sorry, the '747, Allen and
14 other citations were extemporaneous to put
15 oral liquids with such a manner. The pH was
16 about that, about 4.5. In reference to the
17 millimolar powder concentrations going back to
18 what I said earlier about de Villiers.

19 Q. So that concentration of buffer 5 millimolar to
20 20 millimolar, again, would be -- why would a
21 POSA do that?

22 A. Routine experimentation application.
23 Application of known equations in the art to
24 calculate buffer concentrations.

25 Q. I think we covered this one with the paraben or

1 FDA, in order to approve the ready-to-use
2 liquid formulation of enalapril.

3 Q. And a person of ordinary skill in the art

4 A. That's correct yes.

5 Q. -- would be motivated to create a formulation
6 with 24 months stability or shelf life based on
7 what?

8 A. Based, again, on the requirements. In the
9 guidance, the FDA guidance says that in order
10 to approve again this oral liquid formulation
11 it has to have 18 or 24 months stability. It's
12 an easy task for the POSA with a high
13 probability of success using knowledge already
14 in the prior art that we -- that I use in
15 expressing my opinions.

16 Q. Okay. Thank you, Doctor. I want to shift
17 gears now and talk about secondary
18 considerations of nonobviousness, which is part
19 our defense. Plaintiff has the burden to
20 establish those defenses but we want to put Dr.
21 Constantinides on just once.

22 THE COURT: I have a question.
23 Before you shift gears and I may have missed it
24 so if I did point me in the right direction. I
25 asked Mr. Kong, I'm sure you heard, how he was

1 recognize that, Doctor?

2 A. Yes.

3 Q. Did you use that in your analysis in this case?

4 A. Yes.

5 MR. HOGAN: Next slide, please.

6 BY MR. HOGAN:

7 Q. On slide 9, the standard for lack of written
8 description is summarized in this slide. Did
9 you apply this standard in your analysis in
10 this case, Doctor?

11 A. Yes.

12 MR. HOGAN: Next slide, please.

13 BY MR. HOGAN:

14 Q. And summarizing this slide, the enablement
15 standard. Did you apply this standard in your
16 analysis in this case, Doctor?

17 A. Yes, I have.

18 Q. I want to talk about indefiniteness first. Do
19 you have an opinion that one of the claim terms
20 in these patents is indefinite?

21 A. Yes.

22 Q. What is that opinion?

23 A. The word "stable" used in the two inventions,
24 the patents, the '482 -- I'm sorry, the '621
25 which has the same specification with '482 is

1 indefinite.

2 Q. Are you referring to the word "stable" in the
3 preamble or in the wherein clause?

4 A. In the preamble, I'm sorry.

5 Q. Okay. Why?

6 A. Because stable beyond chemical stability
7 includes other stability properties such as
8 physical stability, even chemical stability
9 beyond -- you have an oxidative stability due
10 to hydrolysis, oxidation, further stability,
11 and then in terms of different other types of
12 stability, we're talking about stability in
13 reference to organoleptic properties, taste,
14 smell and color, antimicrobial stability,
15 that's why you have antimicrobial in the
16 formulation. So there are several specific
17 properties under the term "stable," and it has
18 not been defined in the specifications of these
19 patents.

20 Q. Are you referring to the term "stable" by
21 itself?

22 A. Yes, they were stable, yes.

23 Q. What else did you consider in arriving at your
24 view that the word "stable" is indefinite in
25 the '621 patent?

1 indefinite, and then in response actually to
2 the patent office and examiner's rejection, the
3 inventors removed the word "stable" from the
4 '482 patent, but it appears in the '621.

5 Q. Okay. And I think you said earlier you're
6 aware that the specifications of the two
7 patents are the same?

8 A. That's correct. They share a common
9 specification.

10 Q. And you're aware that the '621 is a
11 continuation application of the '482; right?

12 A. That's correct, yes.

13 Q. I want to shift gears for a moment and then
14 focus on written description. Can you
15 summarize your opinion on whether or not the
16 patents in this case have sufficient written
17 description?

18 A. Yes. It lacks written description, yes.

19 Q. Can you summarize why?

20 A. Yeah the written description requirements is in
21 reference to a paraben or a mixture of
22 parabens. I have not seen statements
23 description in the specification where when
24 parabens are used as preservatives you generate
25 a formulation with a 12-month, ready-to-use

1 liquid formulation with a 12, 18, and 24-month
2 stability.

3 Q. Okay.

4 MR. HOGAN: Can I have slide 57,
5 please.

6 BY MR. HOGAN:

7 Q. Okay. So just to clarify for the record,
8 you're talking about the claim element 3 with
9 the paraben or mixture of parabens having shown
10 the characteristics of the wherein clause of
11 this stability characteristic for that amount
12 of time; right?

13 A. That's correct, yes.

14 Q. Okay.

15 MR. HOGAN: Can I have slide 58.

16 BY MR. HOGAN:

17 Q. Okay. These are the tables that appear for the
18 examples in the common specification of these
19 patents. Do you recognize these, Doctor?

20 A. Yes, I do. Yes.

21 Q. Okay. Is it your understanding, sir, that
22 examples A and C are the only examples in the
23 patent that provide exemplary formulations with
24 a paraben or mixture of parabens in them?

25 A. Yes.

1 Q. Now let's look at -- blow up A1 first, please,
2 a little bit. I think as Dr. Little pointed
3 out yesterday the ingredients are on the left,
4 the amounts are on the right, and the existing
5 formulations are on the top A1 through A6. If
6 you look at this table, Doctor, is there any
7 formulation where the preservative is only a
8 paraben or a mixture of parabens?

9 A. No.

10 Q. Okay. Go to table A2 please. Actually, just
11 briefly here at table A2, this is depicted
12 essentially stability at temperature and time,
13 hours on the left and the formulations are
14 across the top, 180 hours is not 12 months;
15 right?

16 A. Yes.

17 Q. Can we go to table C, please. This is table C1
18 from the common specification. Again, looking
19 at these formulations, Doctor, and reading the
20 C1 to C5 across the top. Reading down on the
21 left-hand side there's not a single formulation
22 C1 to C5 where the preservative is a paraben or
23 a mixture of parabens; right?

24 A. Yes.

25 Q. And then go down and we have -- then this is

1 some stability data for the C formulation shown
2 here; right? Correct? Do you see that?

3 A. Yes.

4 Q. And the amount of time is shown in weeks. See
5 that?

6 A. That's correct, yes.

7 Q. And so there's no -- there's no data showing
8 stability of the formulation with the paraben
9 or mixture of parabens as the preservative with
10 stability in this application beyond eight
11 weeks; right?

12 A. Correct, yes.

13 Q. So let's for a second, Doctor, review table --
14 in closer detail table C1. Now do you see
15 formulation C4 -- I'm sorry C3 and C4?

16 A. Yes.

17 Q. So that appears to show the preservative in
18 these formulations includes methylparaben and
19 sodium benzoate?

20 A. Yes, correct.

21 Q. But that's not just a paraben or mixture of
22 parabens, is it? Because there is
23 preservative, sodium benzoate?

24 A. Is not.

25 Q. Can we look at table A1. Same exercise.

1 Looking at these formulations I think it's
2 example A5, it shows an amount of methylparaben
3 sodium. Do you see that?

4 A. Yes.

5 Q. And it also shows an amount of sodium benzoate
6 preservative. Do you see that?

7 A. Yes.

8 Q. And I'm not going to redo this for both patents
9 but the specifications are exactly the same
10 substantially; right?

11 A. Yes.

12 Q. So this argument about -- you're opinions about
13 lack of written description would apply to both
14 patents equally; is that right?

15 A. Correct, yes.

16 Q. Okay so let's shift gears to enablement. Okay?

17 A. Yes.

18 THE COURT: Is this your last piece
19 of your direct?

20 MR. HOGAN: It is, Your Honor.

21 THE COURT: Okay.

22 BY MR. HOGAN:

23 Q. Can you summarize your opinion, Doctor, why or
24 your opinion as to the enablement of the claims
25 of the patent, the asserted patents?

1 MR. KONG: How is that for a range.

2 THE COURT: Could you be more
3 specific?

4 MR. KONG: Hour and 15.

5 THE COURT: About an hour. Let's
6 take a five-minute recess. I want to conclude
7 the cross-examination. I want to get this
8 witness done before the lunch break.

9 MR. KONG: Understood.

10 THE COURT: Let's take a break.

11 (A recess was taken, after which the
12 following proceedings were had:)

13 THE CLERK: Court is in session.

14 THE COURT: Is everyone back. Okay.
15 That's all right. I can wait. Whenever you're
16 ready.

17 CROSS-EXAMINATION

18 BY MR. KONG:

19 Q. Hello, sir.

20 A. Hello.

21 Q. During your direct testimony you offered no
22 opinion regarding inventorship; is that right?

23 A. Correct.

24 Q. During your direct testimony you offered no
25 opinion regarding the indefiniteness of the

1 term buffer; is that correct?

2 A. Correct.

3 Q. During your testimony on direct you offered no
4 opinion regarding anticipation; is that right?

5 A. Correct.

6 Q. You're aware that the Court construed the term
7 consisting essentially of which appears in
8 claim one, the '621 patent; right?

9 A. Yes, I do.

10 Q. In your direct testimony I didn't hear you use
11 the words basic and novel property of the
12 invention; is that right?

13 A. Can you repeat your last question, please.

14 Q. I didn't hear you use the words basic and novel
15 property of the invention; is that right?

16 A. That's correct.

17 Q. I didn't hear you address any of the Court's
18 claim constructions; is that right?

19 A. That's correct.

20 Q. So let's talk about pH. You testified on
21 direct that a pH of 3.3 is approximately three;
22 right?

23 A. Yes.

24 Q. So you would agree that a pH of 2.7 is
25 approximately 3; right?

1 A. Yes.

2 Q. So let's go to PTX 78. I have some binders to
3 hand out.

4 THE COURT: Are any of these in
5 evidence, are they all new?

6 MR. KONG: The three that I'm sure
7 I'm going to cover are new. The rest are in
8 there in case.

9 THE COURT: What are they?

10 MR. KONG: It's PTX 78 is one I'm
11 going to cover right now.

12 THE COURT: PTX 78. All right. What
13 else?

14 MR. KONG: PTX 39 and PTX 38 are the
15 ones.

16 THE COURT: Any objection to the
17 admission of those?

18 MR. HOGAN: No.

19 THE COURT: All right. All of those
20 are admitted.

21 (Thereupon, Exhibits PTX 38, 39, and
22 78 were admitted.)

23 BY MR. KONG:

24 Q. Let's turn to PTX 78, please. You did not
25 discuss PTX 78 during your direct testimony; is

1 Q. So we're on page 275 of the reference; right?

2 A. Yes.

3 Q. The pH of the Casas enalapril formulation was
4 2.55 to 2.78; right?

5 A. Yes.

6 Q. On page 276 there's a section entitled
7 "Stability Studies."

8 Do you see that?

9 A. Yes.

10 Q. And on page 277 there's a discussion regarding
11 the enalapril formulations that were studied;
12 right?

13 A. Yes.

14 Q. It says in the left-hand column on page 277,
15 first full sentence, "For enalapril PEF" -- PEF
16 stands for pediatric extemporaneous
17 formulation; right?

18 A. Yes.

19 Q. "For enalapril PEF the drug content was above
20 the 95 percent until 50 days of study for 5 and
21 25 degrees C increasing below this value only
22 in the case of 40 degrees C."

23 Do you see that?

24 A. Yes, I do.

25 Q. "After three months of study at the three

1 temperature study, drug content of the PEF
2 decreased by 40 percent."

3 Do you see that?

4 A. I do.

5 Q. So at 50 days of study, drug content for the
6 enalapril formulations at pH approximately 3
7 were 95 percent; right? After three months
8 they dropped 40 percent; right?

9 A. Yes.

10 THE COURT: According to the study.

11 MR. KONG: According to the study.

12 BY MR. KONG:

13 Q. So a pH of approximately 3 did not prevent
14 stability from crashing after 50 days; is that
15 right?

16 A. For this particular study.

17 Q. The stability test data presented in Casas at
18 50 days and 5 degrees C is not predictive of
19 drug content at 5 degrees C?

20 A. 25 degrees not 5 degrees. 25, the higher
21 temperature.

22 Q. No. I'm talking about 5 degrees?

23 A. Okay.

24 Q. So I'm going to restate the question. The
25 stability test data presented in Casas at

1 50 days and 5 degrees C is not predictive of
2 drug content at 12 months and 5 degrees C;
3 right?

4 A. Yes, because of the the degradation, the
5 40 percent.

6 Q. The stability test data presented in Casas at
7 50 days and 25 degrees C is not predictive of
8 drug content at 12 months and 5 degrees C;
9 right?

10 A. Yes.

11 Q. So let's switch gears to Allen 1998. This is
12 DTX 1074. This was used on direct. Allen 1998
13 is the primary reference that you rely upon for
14 the pH at which enalapril is maximally stable;
15 right?

16 A. Yes.

17 Q. You rely on the sentence -- I apologize. Let's
18 go to page 1917. At the bottom, thank you, of
19 page 1917, right-hand column, it says that
20 enalapril is reported to have a maximum
21 stability at a pH of about 3; is that right?

22 A. Yes.

23 Q. Okay. Allen didn't do any work to determine
24 the pH at which enalapril is maximally stable;
25 is that right?

1 A. That's correct.

2 Q. And footnote 18 is attached to that sentence;
3 right?

4 A. Yes.

5 Q. And a POA would read the footnote that's
6 attached to the sentence to confirm the
7 content; right?

8 A. Yes.

9 Q. Could you turn to page 1920, please. Footnote
10 18, it references the Merck index; right?

11 A. Yes.

12 Q. So the Merck index is cited for the proposition
13 that enalapril is maximally stable at a pH of
14 about 3; right?

15 A. Yes.

16 Q. Let's turn to PTX 38, please.

17 MR. KONG: This is one of the new
18 exhibits, Your Honor.

19 BY MR. KONG:

20 Q. Do you recognize PTX 38 as the Merck index that
21 is cited in footnote 18?

22 A. Yes.

23 Q. The Merck index is a publicly available
24 document; right?

25 A. Yes.

1 Q. You did not consider the Merck index for
2 purposes of formulating your opinions in this
3 case, did you?

4 A. No.

5 Q. You agree that the Merck index monograph or
6 enalapril that's in PTX 38 does not reference a
7 pH at which enalapril is maximally stable;
8 right?

9 A. Does not -- yes, that's not part of the index
10 anyway. It's not the purpose of the index.

11 Q. Do you agree with my question, sir?

12 A. Yes, I do, yes.

13 Q. Let's move to DTX 1077. This was an exhibit
14 used during direct, the Sosnowska paper?

15 A. Yes.

16 Q. You testified on direct that you relied on this
17 document for the notion that maximum stability
18 of enalapril maleate is a pH of 3; right?

19 A. Yes.

20 Q. Let's turn to page 322, please. So on this
21 page, this is the reference. This is the
22 sentence that you rely on from Sosnowska to
23 support that proposition; right? Right?

24 A. Yes. Sorry.

25 Q. And it cites to footnote 10; right?

1 A. Yes.

2 Q. And footnote 10, if we can go to page 326,
3 cites the same Merck index that we just looked
4 at, PTX 38; right?

5 A. Yes.

6 Q. Let's change subjects and talk about
7 hydrolysis. Enalapril is a prodrug; right?

8 A. Yes.

9 Q. The prodrug enalapril converts into its parent
10 drug enalaprilat; right?

11 A. Yes.

12 Q. You don't think hydrolysis converts the prodrug
13 enalapril into its parent enalaprilat; right?

14 A. Repeat your last question, please.

15 Q. You don't think hydrolysis converts the produg
16 enalapril into enalaprilat; right?

17 A. No. It's metabolism in people.

18 Q. So you agree with what I said; right/

19 A. Yes.

20 Q. In your opinion, whether enalapril is a prodrug
21 or not, it's irrelevant to enalapril's chemical
22 stability in water; right?

23 A. Yes.

24 Q. Okay. Let's talk about your obviousness
25 opinion. It sounds like you're now down to six

1 references; is that right?

2 A. I don't remember the exact number. Yes.

3 Q. '747, the kit insert. Allen 1998, Sosnowska,
4 Nahata, de Villiers, that's six; right?

5 A. Yes.

6 Q. Did I miss any?

7 THE COURT: His testimony was what it
8 was. Go ahead.

9 MR. KONG: Fair enough.

10 BY MR. KONG:

11 Q. Do you agree that none of those references
12 disclose all of the particular concentrations
13 and variations in the asserted claims of the
14 '482 and '621 patents; right?

15 A. Yes.

16 Q. To fill the holes in those references, you rely
17 on the knowledge of a POSA and the notion of
18 routine experimentation; right?

19 A. Yes.

20 Q. Let's discuss some of those holes. None of the
21 references you rely on describe an oral liquid
22 formulation of enalapril that meets any
23 stability limitation of the asserted claims;
24 right?

25 A. Yes.

1 Q. None of your references disclose an oral liquid
2 enalapril formulation that used a claimed
3 buffer concentration; right?

4 A. Yes.

5 Q. You think the claimed buffer concentrations can
6 be obtained through routine experimentation;
7 right?

8 A. Yes.

9 Q. It would take, in your opinion, a POSEA a day or
10 two to perform those experiments; right?

11 A. Yes.

12 Q. And you spent approximately 200 hours working
13 on this case; right?

14 A. I don't recall the exact amount, I mean, I
15 don't know how.

16 Q. Is 200 a fair estimate?

17 A. Probably less -- less than that.

18 Q. 150. You spent 150 hours working on this case;
19 right?

20 THE COURT: Mr. Hogan, will you
21 stipulate that he spent at least 150 hours.

22 MR. HOGAN: Your Honor, I have no
23 idea how much time he spent.

24 THE COURT: Go ahead and ask your
25 question.

1 BY MR. KONG:

2 Q. Is 150 hours a fair estimate of the amount of
3 time you spent?

4 A. I don't know.

5 Q. Why don't we refresh your recollection. Go to
6 page 19 of your deposition, line 9.

7 THE COURT: Just read.

8 MR. KONG: Sure.

9 BY MR. KONG:

10 Q. I asked you approximately how many hours did
11 bill in connection with your opening report.
12 You said fairly comprehensive so I would say
13 approximately 90 hours. Next question,
14 approximately how many hours did you bill in
15 connection with your reply report?
16 Approximately 60.

17 A. Yeah, I said that, yes.

18 Q. So 150 hours is a fair estimate; right?

19 A. Yes.

20 Q. But you didn't take a day to determine the
21 optimal buffer concentration for enalapril
22 formulation?

23 A. Calculations, that's all.

24 Q. But you didn't spend a single day or hour doing
25 it?

1 A. No, I have not. I have not calculated those.

2 No, I have not.

3 Q. Let's talk about stability. In your opinion a
4 person of ordinary skill in the art would have
5 known how to optimize the stability of known
6 enalapril oral liquid formulations to achieve
7 the stability limitations in the asserted
8 claims; right?

9 A. Yes.

10 Q. The '747 patent, Epaned insert, and Allen 1998
11 are the references you combined for purposes of
12 your analysis; right?

13 A. Plus my own experience at least as a POSA.

14 Q. I'm talking about references right now, those
15 are three references you combined; right?

16 A. Yes.

17 Q. Between those three references in your opinion
18 a POSA would start with the Allen reference for
19 purposes of creating a ready-to-use formulation
20 containing enalapril; right?

21 A. Yes, that's what I said. Yes.

22 Q. So let's turn to DTX 1074. This is the Allen
23 reference. The Allen reference was disclosed
24 to the examiner during the prosecution?

25 A. Yes.

1 Q. The enalapril formulation described herein are
2 compounded; right?

3 A. Yes.

4 Q. Moving to page 1920, on the right-hand side
5 under the enalapril maleate on this page Allen
6 provided procedures of the enalapril
7 formulations; right?

8 A. That's right.

9 Q. On the right-hand side column do you see
10 instruction number eight?

11 A. Yes.

12 Q. He says to label the bottle with an expiration
13 date of 60 days; right?

14 A. Yes.

15 Q. And you do not disagree with that instruction;
16 right?

17 A. Can you repeat.

18 Q. You do not disagree with that instruction;
19 right?

20 A. It's meant to be stable for at least about the
21 60 days.

22 Q. Do you disagree with that instruction?

23 A. No, I don't.

24 Q. Allen discusses three compounded enalapril
25 formulations; right?

1 A. Yes.

2 Q. In your opinion you think a POSA would think
3 that the Ora-Sweet SF and Ora-Plus formulation
4 is the best starting point for purposes of
5 developing a ready-to-use formulation
6 containing enalapril; right?

7 A. Yes, based on the stability that are presented.
8 Yes.

9 Q. To do all of us a favor I'm going to call that
10 the SF formulation; is that fair?

11 A. That's fine.

12 Q. In your opinion a POSA would choose the SF
13 formulation as a starting point because of the
14 stability data presented in table two and
15 because the formulation details are within the
16 scope of the asserted claims; right?

17 A. I would not say within the scope of the
18 asserted claims. I would say that at a source
19 of 25 degree stability that can be used to
20 extrapolate longer term stability under
21 refrigerated conditions. So that's what I.

22 Q. That's not what you told me at your deposition.
23 Let's take a look.

24 A. Can we please repeat what I said at my
25 deposition.

1 Q. Sure page 103, line 19.

2 "QUESTION: So a person of ordinary skill
3 in the art would choose the mixture of
4 Ora-Sweet SF and Ora-Plus formulation as a
5 starting point for the development of a
6 ready-to-use formulation containing enalapril
7 because the stability data presented in table
8 two and because the formulation details are
9 within the scope of the asserted claims?"

10 MR. HOGAN: Objection, Your Honor.

11 BY MR. KONG:

12 Q. "Right."

13 "ANSWER: Yes."

14 THE COURT: What's the basis?

15 MR. HOGAN: Objection, Your Honor.

16 THE COURT: Basis?

17 MR. HOGAN: Completeness.

18 THE COURT: You can cover that on
19 redirect. Overruled.

20 BY MR. KONG:

21 Q. Did I read that correctly?

22 A. It says yes.

23 THE COURT: Did he read the
24 deposition right?

25 THE WITNESS: He did, yes.

1 BY MR. KONG:

2 Q. Let's look at table two on page 1918, please.

3 This is the table where Allen displays the
4 stability data associated with all three
5 enalapril formulations; right?

6 A. Yes.

7 Q. So you're a formulation expert; right?

8 A. Yes, I am.

9 Q. And you studied Allen; right?

10 A. Yes.

11 Q. So which of these three present the best
12 stability data?

13 A. The one that shows -- well I will say that 95,
14 there is 95 percent within 60 days is
15 maintained on all of them but the one to one
16 mixture of the Ora-Sweet and Ora-Plus at both 5
17 degrees and 25 degrees is what I will single
18 out in this case out of these.

19 Q. So you think the best stability data on this
20 screen, on this page, excuse me, is the SF
21 formulation; right?

22 A. Yes. It's pretty comparable to me but I think
23 that one, the one to one mixture of the
24 Ora-Sweet and Ora-Plus.

25 Q. So the SF formulation has the best stability

1 data?

2 A. Yes.

3 Q. What has the second best?

4 A. Excuse me.

5 Q. Which has the second best?

6 A. I will say the cherry syrup looks pretty good
7 both at five degrees and 25 degrees. Even
8 after 60 days actually the potency is 97 and 96
9 percent. So that one is also a good candidate.

10 Q. So cherry syrup formulation, that gets second
11 place; right?

12 A. Yes.

13 Q. So let's look at page 1917, the top right-hand
14 corner. This is where it provides the pH of
15 all the formulations and you agree with me that
16 the SF formulation of enalapril maleate had a
17 pH of 4.7 to 4.8; right?

18 A. Yes.

19 Q. And the cherry syrup formulation of enalapril
20 had a pH of 3.9; right?

21 A. Yes.

22 Q. So on a head to head competition the
23 formulation with a pH of 4.8, 4.7, 4.8, that
24 came in first; right? And the pH 3.8 came in
25 second?

1 A. I did not really interpret it that way. I just
2 saw the stability.

3 Q. Did I say that correctly, though?

4 A. Yes.

5 Q. The formulation where pH 4.7 to 4.8 came in
6 first place; right?

7 A. They're pretty close.

8 Q. First place by a nose; right?

9 A. Excuse me.

10 Q. First place by a nose; right? First place by a
11 little bit?

12 THE COURT: If you get him to concede
13 it's fine. Could you please reacclimate me as
14 to how this pertains to the issues in the case.

15 MR. KONG: He testified on direct
16 that pH is what would drive the decision, pH
17 drives stability. So because to obtain maximum
18 stability you want to go to a pH that's as low
19 as possible. Here you have a pH of 4.7, 4.8
20 that did better in a stability study than a
21 formulation that had the pH of 3.9.

22 THE COURT: Remind me what we're
23 looking at here.

24 MR. KONG: This is the Allen
25 reference.

1 BY MR. KONG:

2 Q. If you want to look at at a document that's in
3 front of you I believe you can take a look.
4 I'm not sure where to refer you.

5 A. What DDX is that one?

6 Q. DTX 1094. When you find what you're looking
7 for, let us know.

8 A. Yeah. I have it. Just a second.

9 Yes. That's -- just to confirm whatever,
10 12 weeks was the maximum stability obtained
11 with the oral liquid formulation, the
12 reconstituted oral liquid formulation.

13 Q. So I'll repeat my question. When the powder
14 formulations disclosed in the '747 patent are
15 reconstituted, they do not meet any stability
16 limitation that is claimed; correct?

17 A. Correct.

18 Q. You agree the '747 patent does not identify a
19 target range of buffer concentration for the
20 reconstituted formulation; right?

21 A. Yes.

22 Q. The '747 patent does not identify a target
23 range for pH of the reconstituted powder
24 formulation; right?

25 A. Yes.

1 Q. Let's turn to DTX 1073 which is another exhibit
2 you addressed on direct.

3 A. Right.

4 Q. This is the Epaned insert; right?

5 A. Yes.

6 Q. The Epaned insert describes the Epaned kit
7 product; right?

8 A. Yes.

9 Q. The Epaned kit product was disclosed to the
10 examiner during prosecution; right?

11 A. Yes.

12 Q. If we could move to section 11 of DTX 1073.
13 Looking at the last paragraph that's up here,
14 you agree that the Epaned insert lists the
15 ingredients in the reconstituted formulation;
16 right?

17 A. Yes.

18 Q. The Epaned insert does not identify the amount
19 of citric acid or sodium citrate in the
20 reconstituted formulation; right?

21 A. Yes.

22 Q. The methyl paraben is present in .03 percent
23 and propylparaben in .008 percent; right?

24 A. Yes.

25 Q. You agree with me that potassium sorbate is not

1 a paraben; right?

2 A. It is not a paraben; correct.

3 Q. The Epaned insert does not identify the pH of
4 the reconstituted solution; right?

5 A. No.

6 Q. The Epaned insert does not disclose an oral
7 liquid formulation of enalapril that meets any
8 asserted -- excuse me -- the stability
9 limitation of any asserted claim; right?

10 A. Yes.

11 Q. Let's move to -- it's Bates Number 9315 in this
12 exhibit, section 2.3, last paragraph. Section
13 2.3 instructs users to discard the
14 reconstituted powder formulation after 60 days;
15 right?

16 A. Yes.

17 Q. It instructs users to create a label that says,
18 "Do not use 60 days after reconstitution ";
19 right?

20 A. Yes. It's not meant to be stored longer than
21 that. Use within 60 days.

22 Q. And reconstituted formulation described within
23 the Epaned insert contains mannitol; right?

24 A. Yes.

25 Q. The sweeteners in the reconstituted powder

1 formulation discussed here are sodium
2 saccharin, sorbitol and citrus berry; right?

3 A. Yes.

4 Q. In your opinion, a POSA using Epaned insert as
5 a starting point to make a ready-to-use
6 formulation containing enalapril would not
7 substitute sucralose for sweeteners used in the
8 Epaned insert; right?

9 A. Could you repeat your last question?

10 Q. Sure. In your opinion, a POSA using an Epaned
11 insert as a starting point to make a
12 ready-to-use formulation containing enalapril
13 would not substitute sucralose for the
14 sweeteners that are listed in the Epaned
15 insert; right?

16 A. Yes.

17 Q. Let's move to DTX 1077. This is the Sosnowska
18 paper that you addressed on direct. We talked
19 about this earlier. I have a few follow-up
20 questions.

21 Sosnowska was disclosed to the examiner
22 during prosecution; right?

23 A. Yes.

24 Q. Sosnowska does not disclose an oral liquid
25 formulation of enalapril that meets any

1 stability limitation of the asserted claims;
2 right?

3 A. Yes.

4 Q. You agree that the stability data presented in
5 Sosnowska goes out to only 30 days; right?

6 A. Yes.

7 Q. Sosnowska did not use sodium citrate in either
8 of the two enalapril formulations discussed in
9 the reference; right?

10 A. Yes.

11 Q. Sosnowska used methyl hydro benzoate as the
12 preservative; right?

13 A. Can you please go to the -- let me just review
14 that. What is the PDX, please, number?

15 Q. Sure. The DTX number is 1077.

16 A. Ten, what is --

17 Q. 1077.

18 A. That's all right. Can you repeat the last
19 question, please?

20 Q. Sosnowska used methyl hydro benzoate as the
21 preservative; right?

22 A. Yes.

23 Q. Please turn to DTX 1078. This is the Nahata
24 reference?

25 A. Yes.

1 THE COURT: Ask you next question.

2 MR. KONG: I will.

3 BY MR. KONG:

4 Q. DTX 1118, de Villiers, you discussed this on
5 your direct; right?

6 A. Yes.

7 Q. de Villiers does not disclose a formulation
8 containing enalapril; right?

9 A. Correct.

10 Q. de Villiers does not mention enalapril at all;
11 right?

12 A. Correct.

13 Q. I'm going to shift gears now to your
14 indefiniteness opinion. I'm sorry. There were
15 a couple follow-ups from obviousness that I
16 want to hit on before I do. Forgive me.

17 We're going shift back to the FDA
18 guidance documents which is DTX 1109 that you
19 discussed on your direct. Go to page 5,
20 please. And you discussed on direct section B
21 on this page; right?

22 A. Yes.

23 Q. Just so we're all clear, this document does not
24 explain how one of skill in the art can take an
25 enalapril formulation and make it stable at

1 12 months under refrigerated conditions; right?

2 A. That's not the purpose of any FDA guidance.

3 Q. Thank you. I want to refer you to the
4 statement there that starts if significant
5 change. Do you see that?

6 A. Yes.

7 Q. Okay. So it says, "if significant change
8 occurs between 3 and 6 months of testing at the
9 accelerated storage condition the proposed
10 retest period should be based on realtime data
11 available at the long-term storage condition;"
12 right?

13 A. Correct.

14 Q. And that means you should rely on the
15 refrigerated condition; right?

16 A. For this particular case, yes.

17 Q. Let's go to page nine where it defines the term
18 significant change. Page 11. In the middle
19 there it says in general. Do you see that

20 A. Can you expand that please.

21 Q. It says, "in general significant change of a
22 drug product is defined as one or more of the
23 following." And the first one is a five
24 percent change in assay from its initial value;
25 right?

1 A. Yes.

2 MR. KONG: Your Honor, I promise that
3 will make more sense once more witnesses
4 testify what that means.

5 THE COURT: All right.

6 BY MR. KONG:

7 Q. So now we're on to indefiniteness. Am I
8 correct that your opinion on the term stable is
9 focused only on the '621 patent?

10 A. Yes.

11 Q. I'd like to refer to DDX 054. This is one of
12 the demonstratives you displayed while you were
13 talking about this subject. And you have a
14 couple of excerpts from the '482 patent here,
15 and it shares a specification with the '621;
16 right? The top one discusses enalapril oral
17 liquid formulations; right?

18 A. Yes.

19 Q. Okay. And this is PTX 1 at column 18, line 39.
20 After that first sentence there's a definition
21 of the term stable; right?

22 A. Chemical stability only, this particular
23 definition.

24 Q. There's a definition of the word stable as used
25 in this patent; right?

1 A. Yes.

2 Q. And on the bottom you highlighted another
3 definition of the word stable. Do you see
4 that? But you deleted the text that comes
5 right before it. Do you see that? Why did you
6 delete the text that comes before?

7 A. I deleted the text.

8 Q. Yeah, so that's another part of the
9 specification there; right? Did you know that
10 was deleted?

11 A. I don't know.

12 Q. Let's see what text is there then. If we can
13 go to column 23, line 19 of PTX 1, please,
14 Bill. So here we can see the full sentence,
15 right? The sentence that proceeded what you
16 were I citing to says, "the enalapril powder
17 formulations;" right?

18 A. Yes.

19 Q. That's discussing enalapril powder
20 formulations?

21 A. Correct.

22 Q. Not an enalapril liquid formulation; right?

23 A. Yes.

24 Q. So if we go back to DDX 50. 54, excuse me.
25 You agree that the excerpt on top here is

1 discussing the enalapril liquid formulation.

2 The excerpt on the bottom is discussing powder
3 formulations; right?

4 A. Correct.

5 Q. And the word stable has a different meaning
6 depending on which formulation you're talking
7 about; right?

8 A. But the same requirements apply to both when it
9 references stability. So the fact that they
10 share the powder formulation and the liquid
11 formulation, they share a common drug substance
12 or API, active pharmaceutical ingredient, in
13 this case the enalapril maleate, is that
14 whatever knowledge you have of stability with
15 the powder formulation a POA can use to
16 develop stable oral liquid formulation. If the
17 powder stability shows 18 months or 24 months
18 that will be the objective of the POA with a
19 task to develop ready-to-use liquid
20 formulation.

21 Q. The definition on top appearing at column 18,
22 line 39 of the word stable, that applies to
23 liquid formulations; right?

24 A. Yes.

25 THE COURT: You've already

1 established that.

2 BY MR. KONG:

3 Q. And you agree with me that the definition of
4 stable at column 23, line 22 applies to powder
5 formulations; right?

6 THE COURT: You've already
7 established that.

8 MR. KONG: Thank you.

9 BY MR. KONG:

10 Q. And you agree with me the claims here, the
11 asserted claims of the '621 are directed to
12 liquid formulations?

13 A. Yes, I do.

14 Q. Thank you. So let's talk about written
15 description. In your opinion the claim
16 limitation requiring 12 month stability at
17 refrigerated conditions must be supported by
18 stability data at 12 months under refrigerated
19 conditions; right?

20 A. Yes.

21 Q. Same question, substitute the number 18 in for
22 the number 12, same answer?

23 A. But written description and definition, again,
24 to using using paraben or a mixture of
25 parabens. I'm not sure what.

1 Q. I'll ask the full question. In your opinion
2 the claim limitation requiring 18 months
3 stability at refrigerated conditions must be
4 supported by stability data at 18 months under
5 refrigerated conditions; right?

6 A. Yes.

7 Q. Same question, substitute the number 24 in for
8 18, same answer?

9 A. Yes.

10 Q. Let's move to enablement. During your direct
11 examination I didn't hear you address the wands
12 factors, W-A-N-D-S; correct?

13 A. Yes.

14 THE COURT: What's that?

15 MR. KONG: It's a legal standard.

16 THE COURT: Wands.

17 MR. KONG: W-A-N-D-S, a legal
18 standard for enablement.

19 THE COURT: Do you want to tell me
20 what it is or not?

21 MR. KONG: It's an eight or nine
22 factor test for enablement set forth by the
23 federal circuit and it's followed pretty
24 regularly when it comes to enablement.

25 THE COURT: That's good enough. Go

1 MS. HANSON: Long-felt need, Your
2 Honor.

3 THE COURT: Excuse me?

4 MS. HANSON: Long-felt need, the
5 long-felt but unmet medical need in this field.

6 THE COURT: And this goes to the
7 issue of obviousness.

8 MS. HANSON: Obviousness, yes, this
9 is an objective indicia of obviousness so we're
10 rebutting their obviousness case.

11 THE COURT: Understood. Is there an
12 agreement or objection by defendant regarding
13 his expertise or opinion as a proffer?

14 MR. KRATZ: None whatsoever.

15 THE COURT: Okay. So same thing I
16 said to other counsel. Feel free to lead him
17 through his CV and then go ahead.

18 MS. HANSON: Thank you, Your Honor.

19 DIRECT EXAMINATION

20 BY MS. HANSON:

21 Q. Good afternoon, Dr. Mahan. Would you please
22 introduce yourself to the Court.

23 A. Yes. My name is John D. Mahan, M.D.

24 MS. HANSON: If we could look at PTX
25 105, please, Mr. Smith.

1 BY MS. HANSON:

2 Q. Is this your CV?

3 A. Yes.

4 Q. So we all agree you're a pediatric
5 nephrologist. Can you please tell us what that
6 means?

7 A. So a pediatric nephrologist is a doctor with
8 special training to -- in the care of children
9 with acute and chronic kidney diseases and also
10 in pediatric hypertension.

11 Q. And what type of conditions does enalapril, the
12 drug at issue here, treat?

13 A. Mainly hypertension. There are some other
14 issues, but mainly hypertension. Certainly in
15 pediatrics, that's the common use.

16 Q. Do you treat patients with enalapril?

17 A. Every week.

18 MS. HANSON: If we could take a look,
19 please, at slide PDX 202.

20 BY MS. HANSON:

21 Q. Where did you go to school?

22 A. So I graduated from La Salle College and
23 received my M.D. from Hahnemann Medical
24 College, now known as Drexel University, in
25 1977. I went on to do my residency in

1 pediatrics, chief residency in pediatrics, and
2 my pediatric nephrology fellowship at the
3 University of Minnesota. I graduated there in
4 1984 and took a position as faculty at the Ohio
5 State University College of Medicine, and I
6 stayed there since in a variety of different
7 positions. And throughout this time I've
8 continued to see patients and take care of
9 patients on a regular basis.

10 Q. What are your current positions? You mentioned
11 that you still practice?

12 A. Yes, I still practice. I'm the director of the
13 pediatric nephrology fellowship training
14 program. I'm also the director of the
15 Nationwide Children's Hospital Center for
16 Faculty Development. That's our children's
17 hospital associated with the university. I'm
18 also a research investigator in the Nationwide
19 Children's Hospital Research Institute, and I'm
20 a professor of pediatrics in the college of
21 medicine.

22 MS. HANSON: If we could go to the
23 next slide, please, 203.

24 BY MS. HANSON:

25 Q. How many clinical trials have you run?

1 A. I've been a principle investigator in 20
2 clinical trials in pediatrics, the majority of
3 those being pediatric hypertension but also
4 including medications involved in pediatric
5 dialysis and transplantations and bone disease,
6 and I've participated in over 25 studies as a
7 coinvestigator during this time.

8 Q. Have you published any papers?

9 A. Yes. I've had the good fortune to work with
10 good people and had the able to publish 180
11 peer-reviewed publications in various areas of
12 pediatrics and pediatric kidney disease and
13 medical education, also had the chance to
14 author and coauthor 30 book chapters in these
15 fields and also publish 140 abstracts, many of
16 which have been presented at national and
17 international meetings.

18 Q. If we could look back at PTX 105 at the top of
19 page 3, it says here there are a number of
20 honors listed. Please tell us, are any of
21 these particularly notable?

22 A. Well, certainly proud of having the outstanding
23 teacher of the year award several times in the
24 department of pediatrics in the college of
25 medicine and also boards from the children's

1 hospital as well as the college of medicine. I
2 think the two that I'm most proud of is the
3 ACGME Parker Palmer Courage to Teach Award
4 which is awarded to ten individuals in the
5 United States each year with outstanding
6 contributions in graduate medical education and
7 also my recent selection for the American
8 Academy of Pediatrics Henry Barnett award which
9 embodies Henry Barnett's passions, which were
10 clinical care, research, education and
11 advocacy.

12 Q. If we could go back very quickly to slide PDF
13 202. It says here that you cofounded the
14 Pediatric Nephrology Research Consortium. What
15 is that?

16 A. So this is a group of pediatric nephrologists
17 now from 90 centers throughout the United
18 States that have agreed to come together and
19 pursue collaborative clinical research in
20 pediatric kidney disease. I was one of the
21 cofounders in this group in 2003, and I
22 presently serve as board president for our
23 board of directors, and we have published over
24 60 papers now since our inception in pediatric
25 nephrology topics.

1 Q. Let's take a look, please, at slide PTX 204.

2 What is hypertension?

3 A. Hypertension is blood pressure being elevated
4 above the normal range and when the blood
5 pressure is elevated above the normal range,
6 that puts stress in particular on the blood
7 vessels and the heart. As a result of this
8 stress, there can be a number of acute or
9 chronic complications or problems that can
10 ensue. In particular some of the most
11 prominent ones are listed in this cartoon.
12 With that high pressure on the blood vessels,
13 you can develop blood vessel damage over time
14 which can lead to vascular disease. A
15 particularly bad manifestation would be a
16 broken blood vessel anywhere in the body, but
17 in the brain causing a stroke and that can be
18 related to high blood pressure. You can even
19 have acute or chronic visual problems because
20 of high blood pressure damage to the blood
21 vessels in the eye.

22 Because of the stress on the heart,
23 individuals with high blood pressure can
24 develop heart failure and even have heart
25 attack or myocardial infarction. And then the

1 kidneys take a beating. So the kidneys within
2 the setting of high blood pressure develop
3 scarring over time. High blood pressure is one
4 of the leading causes of kidney failure in the
5 United States today.

6 Q. Who is at risk of developing hypertension?

7 A. Everybody. We tend to think of this as an
8 adult problem, but we see hypertension in
9 children, and we see hypertension in the
10 smallest of children. And this constellation
11 of clinical consequences depicted on this
12 diagram I have seen in children, each of these
13 in various formats, and these can be
14 life-threatening and certainly disabling
15 manifestations of high blood pressure.

16 Q. What type of drug is enalapril?

17 A. Enalapril is what's called an ACE inhibitor.
18 As mentioned earlier, this angiotensin can
19 boost ACE enzyme inhibitor, ACE. So I'll use
20 the word "ACE" because I don't want to keep
21 stumbling over angiotensin-convertase enzyme.
22 As an ACE inhibitor, it has an impressive
23 effect of lowering blood pressure because of
24 where it fits into a major driver of high blood
25 pressure in children and adults.

1 Q. Was enalapril the first ACE inhibitor?

2 A. Not the first. It was actually the second.

3 The first one was a medication called captopril
4 with a short half-life. When I was a fellow,
5 we were actually beginning the first pediatric
6 trials of captopril. I remember measuring
7 blood pressure in these kids one hour, two
8 hours after they got the captopril, and it was
9 amazing to see the blood pressure come down in
10 children with high blood pressure. That was
11 the first agent, but because of the short
12 half-life, when enalapril came to the market in
13 1985, that became the go-to medication because
14 it could be given once or twice a day with good
15 results.

16 Q. So let's take a look at slide PDX 205. How
17 does an ace inhibitor treat hypertension?

18 A. Well, this is a good example, and it really
19 starts with the kidney. As I mentioned, the
20 kidney is inevitably involved in hypertension.
21 In most cases of hypertension, there is high
22 levels of a compound called renin being
23 elaborated by the kidney. That renin molecule
24 ends up circulating through the body. And in
25 this diagram of this red tube representing a

1 blood vessel, we can see where renin generates
2 a compound calls angiotensin 1, which is then
3 acted upon by the angiotensin-convertase enzyme
4 to elaborate the potent molecule angiotensin 2.

5 Angiotensin 2 is the bad actor here. It
6 leads to tightening of blood vessels, and it
7 also leads to secretion of a molecule called
8 aldosterone which leads to water and salt
9 retention. So ACE has this pivotal role of
10 lining the blood vessels of generating this
11 angiotensin 2, which is the bad actor.

12 Q. Can you please show us in the next slide where
13 enalapril interrupts the cycle.

14 A. This is the beauty of enalapril and the ACE
15 inhibitors is that it's able to act right there
16 in the center of this cycle and by doing such
17 minimizing or preventing the elaboration of
18 angiotensin 2 and thereby preventing the
19 tightening of the vessels or stretching and
20 secretion of aldosterone, thereby lowering the
21 blood pressure on a reliable basis.

22 Q. So what opinions are you offering here today?

23 A. So I'm prepared to put forth two opinions. The
24 first opinion is that as of March 18, 2016,
25 there was an unmet need for a stable oral

1 liquid formulation of enalapril for children
2 that did not require any type of compounding,
3 reconstitution, or other manipulation before
4 administration. And, secondly, that the
5 claimed inventions and Alkem's ANDA product
6 meet this unfelt need.

7 THE COURT: I'm sorry. Say the last
8 sentence again.

9 THE WITNESS: That both the claimed
10 inventions and Alkem's product meet this unmet
11 need.

12 BY MS. HANSON:

13 Q. Let's take a look, please, at slide PDX 207.
14 What legal standards did you apply in forming
15 your opinions?

16 A. I understand the long-felt need standard would
17 involve the fact that the long-felt and unfelt
18 need is satisfied by the claimed invention as
19 of the date it was claimed and invented, and
20 that the claimed invention must be reasonably
21 commensurate or match the need.

22 Q. What is your understanding as a medical doctor
23 of the claimed invention in this case?

24 A. My understanding as a physician is the claimed
25 invention is to have a stable oral liquid

1 formulation of enalapril that has a stability
2 of 12 months or greater.

3 Q. Can we, please, take a look at PTX 1 and PTX 2.
4 Dr. Mahan, did you review the patents in
5 forming your opinions in this case?

6 A. Yes.

7 Q. And did you review the claims that Azurity
8 asserts Alkem infringes here?

9 A. Yes.

10 Q. How did you develop your opinions with respect
11 to long-felt need in this case?

12 A. So I generated my opinions based on my over
13 40 years of experience in treating children
14 with hypertension, also my reading of the
15 medical literature and review of relevant
16 recent literature, also my review of the
17 patents and my discussions with someone with
18 formulation expertise, in other words,
19 Dr. Little.

20 Q. And did you hear yesterday when Dr. Little
21 offered testimony regarding a person of skill
22 in the art?

23 A. Yes.

24 Q. Can we take a look, please, at slide PDX 208.
25 Have you offered a definition of a person of

1 skill in the art in this case?

2 A. Yes. And in addition to the first three bullet
3 points which was the items that Dr. Little
4 identified, I would offer that an additional
5 aspect of a person of ordinary skill in the art
6 would be someone who routinely collaborates
7 with a medical doctor having experience in the
8 condition, in this case treating hypertension.
9 So I believe I can serve a role as part of that
10 POSA team by being that physician that has the
11 clinical experience and expertise.

12 Q. You mentioned that you use enalapril to treat
13 hypertension. What does the literature say
14 regarding pediatric hypertension?

15 A. It's a growing problem and it is only getting
16 more common, partly due to our successes in
17 medicine, and partly due to our successes in
18 providing more calories than people need in
19 society.

20 Q. Let's take a look at PTX 119. What does this
21 reference?

22 A. This is a recent chapter in a textbook called
23 "Pediatric Hypertension" edited by Joseph
24 Flynn. This is by my mentor in medical school,
25 this is Dr. Falkner who actually got me excited

1 about pediatric hypertension and kidney
2 disease, little did she know, and she's still
3 on the faculty at Temple by the way. This
4 chapter outlines the development of the concept
5 of hypertension in children, really points out
6 that until 1970 we did not even have standard
7 definitions of what was an elevated blood
8 pressure at a different age. So Dr. Falkner
9 details how starting with the NIH task force
10 defining hypertension we began to note kids
11 with high blood pressure and began to identify
12 children who should be treated and follow the
13 epidemiology of hypertension since that time.

14 Q. Have there been any studies to determine the
15 prevalence of pediatric hypertension?

16 A. Yes. And I think our next chapter.

17 Q. So let's take a look at PTX 144, please. And
18 please tell us what does this reference?

19 A. So this is a chapter by Carrie Redwine in that
20 same textbook of "Pediatric Hypertension." The
21 title is "Epidemiology of Primary Hypertension
22 in Children." And Dr. Redwine goes through the
23 factors that have explained the epidemic of
24 hypertension over the last 30 years in our
25 society in great detail.

1 Q. Let's take a look, please, at Bates ending in
2 9546. If we could call out about halfway down
3 down this page. What does Dr. Redwine say
4 regarding the prevalence of pediatric
5 hypertension?

6 A. Dr. Redwine points to literature that suggested
7 about five percent of children and adolescents
8 back in the early 2000s had hypertension and
9 that was certainly a problem and was part of
10 why medications were being developed for
11 children because it was a growing concern. She
12 also points out that more recently in 2014 a
13 meta analysis, which is a compilation of
14 studies that have been done looking in this
15 case at hypertension in children, now show a
16 prevalence rate of 11.2 percent, meaning that
17 11 percent of children in the United States
18 today have high blood pressure based on these
19 findings.

20 THE COURT: We're not disputing the
21 problem; right? Pediatric hypertension.

22 MS. HANSON: No.

23 THE COURT: So why -- I'm not saying
24 you shouldn't be doing this. I just want to
25 follow what you're doing.

1 MS. HANSON: Absolutely, Your Honor.

2 THE COURT: The other side, they have
3 a product they want to get on the market that
4 is about this problem. What is the point of
5 this?

6 MS. HANSON: So the point of this is
7 to establish the fact that there are a lot of
8 kids that have hypertension.

9 THE COURT: So stipulated. I
10 guarantee they'll agree.

11 MS. HANSON: And this is the last
12 slide we're going to talk about with this.
13 Next we're going to go into the therapeutic
14 options that were available. Why the were
15 challenging, what was needed.

16 THE COURT: It's not about long-felt
17 need to address hypertension in kids.

18 MS. HANSON: Yes.

19 THE COURT: It's a long-felt need to
20 produce the product that your client produced;
21 right?

22 MS. HANSON: Yes.

23 THE COURT: So we're getting there;
24 right?

25 MS. HANSON: Very quickly, Your

1 Honor.

2 BY MS. HANSON:

3 Q. You mentioned this earlier, what's contributed
4 to the prevalence of pediatric hypertension in
5 the country today?

6 A. So it's been driven by the increase in obesity
7 and unfortunately many children as well as
8 adults with obesity develop high blood
9 pressure. But also related to our successes in
10 having children with serious medical conditions
11 survive and many of those kids, including
12 premature children, will have kidney injury and
13 high blood pressure as a lifelong problem.

14 Q. Let's take a look at PTX 114. What does this
15 reference?

16 A. This is a review by Chu and colleagues of the
17 available antihypertensive drugs for children
18 and adolescents as of 2014.

19 Q. The taking a look at table two, please, on
20 Bates ending in 9238. What does this show you?

21 A. This is a table of antihypertensive drugs that
22 were started in pediatric clinical trials and
23 were FDA approved. And as you can see the
24 first drug class mentioned is the
25 Angiotensin-converting enzyme inhibitor group,

1 the ACE inhibitors and enalapril is listed up
2 top. If you look at the column on the right
3 you'll see that in terms of pediatric
4 indications from the FDA, enalapril is the only
5 drug that has this broad age range and in fact
6 is indicated down to one month of age for
7 pediatric hypertension.

8 Q. I think we already established in some other
9 testimony that enalapril has been available
10 since 1985. Were you using enalapril to treat
11 pediatric patients before there was an oral
12 liquid product on the market?

13 A. Yes. Because it worked and we needed
14 medications that would work in this children.
15 So shortly after Vasotec, the brand of
16 enalapril, came out in the mid 80s we were
17 starting to give it to kids because we had
18 nothing else and, again, it worked and we
19 unfortunately had to learn a lot along the way
20 and then when we would have children who were
21 not able to swallow tablets we would come up
22 with workarounds. We would have parents put
23 half the tablet in a cup and crush it with a
24 spoon and put some liquid in and give half the
25 liquid. So we would come up with a variety of

1 workarounds including having local pharmacies
2 and hospital pharmacies doing compounding.

3 Q. Let's take a look please at PTX 164. What does
4 this reference?

5 A. This is a review from Zajicek and colleagues
6 representing the national institutes of health
7 as well as the FDA and they looked at the state
8 of pediatric formulations in this task force
9 and sort of reviewed what were the present
10 status and the challenges as of this
11 publication in 2013.

12 Q. So let's take a look, please, at Bates ending
13 in 6891, and if we could pull up the bottom on
14 the right-hand column. What does Dr. Zajicek
15 say regarding developing liquid dosage
16 formulations?

17 A. Not surprisingly they identified that when
18 developing liquid dosage forms, both solubility
19 and stability are critical to designing the
20 appropriate product and furthermore they
21 posited that, the goals, would be to have
22 products with long term stability and they
23 identified at least 18 months of shelf life as
24 the appropriate goal for commercial products.

25 Q. As a doctor do you agree with this?

1 A. Certainly and we certainly recognize the
2 advantages to the patient and the family to
3 have medications that have a long shelf life so
4 that families are not having to go back to
5 pharmacies frequently, potentially running out
6 of the medicine and having to skip doses and
7 other problems that come from short shelf life
8 medications.

9 Q. Let's take a look please at PTX 113 and in
10 particular we're going to look at the article
11 ending in Bates 8015.

12 A. Yes. This is a pharmaceutical technology
13 publication and this is actually an interview
14 or commentary on the issues around pediatric
15 formulations and the same doctor, Zajicek, who
16 works for the NIH came up with I thought a very
17 apt phrase, which is it's by bizarrely
18 primitive the way we take care of oral
19 medications in liquid form for childred in our
20 society.

21 Q. So let's look, please, at the patent here PTX
22 1, and in particular column five pulling out
23 lines 33 to 53. Does the patent here comment
24 on what we call extemporaneous compounding?

25 A. It certainly does and it talks about some of

1 the challenges of extemporaneous compounding in
2 particular the variability in dosing when
3 you're crushing tablets and mixing it with
4 liquid, whether it's done by a family or a
5 local pharmacy the fact that there can be
6 mistakes in dosing due to human error is
7 unfortunate but real. The powder when done
8 this way may not solubilize completely so you
9 may end up not have distribution of medicine
10 throughout the liquids and that can lead to
11 dose to dose variation which can be quite
12 dangerous with blood pressure. And then the
13 issues around instability in these
14 extemporaneous forms, and then the fact that
15 different pharmacies will do it differently.
16 So a family might got to a pharmacy one time,
17 get a prescription, go to a different pharmacy
18 and get something made up differently and not
19 realize the difference, which again is really a
20 potential problem. And lastly the fact that
21 when things are compounded the contamination
22 worries, for example, Mike Beckloff talked
23 about yesterday.

24 THE COURT: What's the primary way to
25 diagnose hypertension in kids?

1 THE WITNESS: You have to measure the
2 blood pressure and so that without measuring,
3 you would not know it, but it's routine
4 practice in hospitalized patients, ER visit
5 patients, and even now in the pediatricians'
6 offices during well-child visits. They measure
7 the blood pressure.

8 THE COURT: When an unacceptable
9 level of blood pressure is detected and
10 enalapril is given, what's the -- what's the
11 dosage that's written on the product that the
12 pharmacist gives to the parent?

13 THE WITNESS: So the prescribing
14 physician would start typically at a dose of
15 0.1 milligram per kilogram. So as a
16 pediatrician, we recognize that medications are
17 best delivered based on the body weight. So I
18 look at the child's weight, calculate out
19 amounts. So I might come up with a dose of
20 1.65 milligrams for this kid. In terms of
21 pills, the smallest pill might be a 2.5
22 milligram tablet.

23 THE COURT: I'm talking about the
24 patent, the liquid.

25 THE WITNESS: Yeah. So with the

1 liquid now, I can give the exact amount of
2 liquid to give the 1.65 milligrams of whatever
3 the amount is.

4 THE COURT: How typically -- I guess
5 it could depend on the level of the problem.
6 Is it given once a day? Is it given three
7 times a day? Is it given over the course of
8 two weeks? Is it given -- does the patient
9 have to take it for a lifetime? How does that
10 work?

11 THE WITNESS: So enalapril in
12 children has a half-life of 12 to 24 hours.
13 Typically, we give it twice a day to get really
14 good results. And for most children, we're
15 talking about hypertension being a chronic
16 condition, so they're taking it the rest of
17 their lives. There are some situations where
18 there's acute kidney injury and they recover
19 and they can come off of that medicine. But
20 the great majority are on this medicine for the
21 rest of their lives.

22 THE COURT: I guess that goes to the
23 necessity to have shelf life, if that's the
24 right word.

25 THE WITNESS: The longer shelf life

1 makes a big difference. Yeah, for a family,
2 going back to the pharmacy every four weeks or
3 eight weeks increases the risk that doses will
4 be missed.

5 BY MS. HANSON:

6 Q. Thank you. Can we take look, please, at PTX
7 125.

8 And we were talking about some of the
9 drawbacks, and in particular, you mentioned
10 there can be issues with the compounding
11 pharmacy. What does this reference?

12 A. This is a review by Gudeman and colleagues on
13 the potential risk of pharmacies doing the
14 compounding, the pharmacy compounding of oral
15 liquid medications.

16 Q. So let's take a look at Bates Number 6630,
17 ,please. There's a column on the right-hand
18 side with a header.

19 How did Gudeman contribute to your
20 understanding here?

21 A. This is actually a paper that reviews the
22 literature on the error rate of compounding by
23 pharmacies. And in two separate studies that
24 Gudeman quotes where the FDA actually went out
25 and got samples that were made by local

1 pharmacies, the error rate was amazing.
2 34 percent of the samples were -- had dosage
3 errors in one study and 33 percent in the other
4 study. Having an error rate of 33 percent is
5 entirely unacceptable in medicine. Our goal is
6 to get error rates down to zero, and this is
7 certainly a preventable error, the fact that
8 the local pharmacy, doing the best they could
9 do, always trying to do a good job, would have
10 products that were wrong this often.

11 THE COURT: Maybe this is a concern I
12 shouldn't concern myself with. A lot of
13 studies and articles have been really flying by
14 here, and they're extensive. And defense
15 counsel, Alkem's counsel, agreed to their
16 admission, but they're all hearsay. So I guess
17 is there -- do all the lawyers agree that these
18 aren't admissible as substantive evidence, or
19 are we skirting the hearsay rules? How is this
20 working? Because there's so much now --
21 there's so much information in this record now
22 about, you know, this ailment. I'm just -- I
23 want to try to keep the record manageable. So
24 what's your view on this?

25 MS. HANSON: My view, Your Honor, is

1 that Dr. Mahan is here testifying as to his
2 experience with this. He's reviewed this
3 literature, he agreed with this literature, and
4 he's testifying as to the long-felt need
5 because there was this prevalence of pediatric
6 hypertension --

7 THE COURT: Hearsay rules allow an
8 expert to rely on information in forming an
9 opinion. My concern, which I should probably
10 just stay out of your way, but my concern is
11 now, are you going to use all of these exhibits
12 as substantive evidence? If you are, I think
13 we need to talk about that. Or are you going
14 to say, look at -- what are we on here? What's
15 this?

16 MS. HANSON: This is PTX --

17 THE COURT: Let's talk about PTX 113,
18 "Technology and Applications," PFQ. I don't
19 know, you've got now -- there's 50 pages of
20 information that this witness did not author.
21 So how do you intend to use these documents?

22 MS. HANSON: So for the one that Your
23 Honor just spoke to --

24 THE COURT: All of them. How do you
25 intend to use them?

1 MS. HANSON: With the testimony that
2 he's providing here today.

3 THE COURT: Okay. And you're not
4 objecting. Why? You're agreeing that they're
5 admissible. Why?

6 MR. KRATZ: I want to make two
7 statements. The first is I'm agreeing they're
8 admissible in support of the expert's opinion.
9 Most of them I'm not concerned with.

10 THE COURT: And Plaintiff's counsel
11 is shaking your head yes. So to sort of shut
12 the conversation and continue on, I'll stay out
13 of your way again. In my view, these are not
14 substantive evidence, and I don't want them
15 used that way when you ask me to render a
16 verdict in your favor or your favor. Okay?

17 MR. KRATZ: The second comment, if I
18 may, is that the prior art for obviousness is
19 different because a prior art reference is
20 offered for the full scope of what's understood
21 by a reader of that art, so for all it teaches
22 is the standard for that piece of art. But
23 prior art is different.

24 THE COURT: Okay. I get that. I get
25 that, but this is not -- this is not --

1 MR. KRATZ: We're okay with it.

2 THE COURT: Is this prior? Is
3 everything he's talking about that talks about
4 the need for the drug and the invention, is
5 that prior art?

6 MS. HANSON: Not for the obviousness
7 case, Your Honor.

8 THE COURT: It's not. It doesn't
9 seem to be prior art to me. It seems to be
10 more backup for why there's a long-felt need
11 for your client's product. Do you agree with
12 that statement?

13 MS. HANSON: I agree with that
14 statement.

15 THE COURT: Okay. So without
16 belaboring it further, I don't view, unless you
17 convince me otherwise, that all these
18 periodicals are fair to game to me for
19 substantive evidence because they're hearsay.
20 Do you disagree?

21 MS. HANSON: I do disagree to the
22 extent that he's testified about certain
23 sections of each of these.

24 THE COURT: It doesn't cure the
25 hearsay problem just because he's testified

1 about them. He's going to say he relied on
2 them to form his opinion. I know that sounds
3 like I'm splitting hairs. I think with a
4 record that's -- I mean, I've got a mountain of
5 information over there -- with a record that
6 you're, by the way, going to have to present in
7 an understandable, concise way. I just -- I'm
8 trying to keep control over the information
9 that's coming in, and I view this as hearsay.

10 MS. HANSON: Your Honor, he will not
11 be -- we will not be citing in post-trial
12 briefing to sections of these documents that
13 Dr. Mahan has not spoken to today and that he
14 is not saying, you know, especially with
15 respect to the studies, that he reviewed relied
16 on in his opinion that compounding was not
17 meeting the needs of these children. That is
18 the underlying --

19 THE COURT: Just because he has
20 testified about them, is it your view that
21 makes them substantive evidence?

22 MS. HANSON: It's my view that his
23 opinion as to the unmet need here is
24 substantive evidence.

25 THE COURT: Agree?

1 MS. HANSON: In forming that opinion,
2 he relied on --

3 THE COURT: There you go. We're
4 saying the same thing. If he relied on it, but
5 that doesn't mean it's substantive evidence.
6 His opinion is substantive evidence.

7 MS. HANSON: Yes.

8 THE COURT: But just because he read
9 15 separate documents doesn't mean that you can
10 say, ah-ha, look this isn't obvious because
11 this doctor, not this witness, said this in
12 page 54 of his report. Consider that
13 substantive evidence.

14 Okay. Do you understand what I'm saying?

15 MS. HANSON: Yes, Your Honor.

16 THE COURT: Okay. Go ahead.

17 BY MS. HANSON:

18 Q. So let's go back to what clinical problems
19 arise with respect to inappropriate dosing?

20 A. So problems that we have seen and have happened
21 in our patients is that patients get doses that
22 are not what we prescribed. If a child gets a
23 dose that's too high compared to what we
24 prescribe for the hypertension drug, the blood
25 pressure will be too low, and we've had parents

1 calling and saying we are getting low readings,
2 and we have to end up looking back and seeing
3 what was going on with the medication and the
4 extemporaneously compounded medication.

5 We've had patients call us and say, "I'm
6 not getting a good result with -- you know, the
7 pressures are high." And we have to be
8 concerned that it's related to the compounded
9 product.

10 I can talk about one patient of mine, a
11 one-year-old with kidney injury, hypertension,
12 on enalapril at home being formulated by the
13 parents from pills, giving a liquid. They
14 started the call saying the pressures were
15 high. We ended up having the child go in to
16 the local pediatrician. Pressures are high.
17 We admit the child, embark on evaluation to see
18 what's going on with the kidneys. Are they
19 getting worse? Meanwhile, we put the child on
20 the same medication program that the child was
21 on at home, in this case being prepared by the
22 nurse on the floor, and lo and behold, the
23 kid's blood pressure normalizes.

24 So well-meaning parents were making a
25 mistake, and that was the state of the art, was

1 these kinds of errors which were things that we
2 saw not infrequently and really did concern us.

3 Q. Let's take a look, please, at PTX 149. What is
4 this reference?

5 A. So this reference, I think, underscores one of
6 the problems. This is Rood's review looking at
7 variability in compounding of the oral liquids
8 for pediatric patients. She confirms what we
9 see in our region in central Ohio. They looked
10 at 244 pharmacies in Michigan and asked the
11 pharmacies how they made up different oral
12 formulations for pediatric patients. And we
13 looked at what they found in particular.

14 Q. Can we take a look --

15 A. Yes.

16 Q. -- please, here on Table 2 at Bates ending in
17 6721?

18 A. If we take a look, in the state of Michigan at
19 this time, there were six different
20 concentrations of liquid enalapril being
21 developed by different pharmacies which meant
22 that there were six different concoctions, so
23 to speak, with different amounts.

24 And this certainly underscores the
25 problem that we saw where results would be

1 variable in children and one of the worries was
2 that one pharmacy made it up differently than
3 the next pharmacy, and that could underlie the
4 problems we were getting in responses to our
5 patients.

6 Q. Could we stake a look, please, at PTX 137.
7 What does this reference?

8 A. So this is Meyers and Siu's paper looking at
9 pharmacotherapy of chronic pediatric
10 hypertension.

11 Q. And if we could take a look at the Bates ending
12 in 3873, did Dr. Meyers look at enalapril in
13 this paper?

14 A. Yes. So in this paper as in 2011, enalapril
15 was one of the medications highlighted, and
16 they provided dosing recommendations for
17 newborns as well as infants and children and
18 adolescents and highlighted the fact that for
19 those children, the only thing available in
20 terms of a liquid were oral suspensions that
21 were extemporaneously formulated.

22 Q. And looking at the Bates ending in 3890, if we
23 go to the second column there. What does
24 Dr. Meyers indicate regarding treatment options
25 for her pediatric patients?

1 A. They talk about the fact that the practitioners
2 have to rely on extemporaneous preparations
3 that were compounded through a variety of
4 different recipes and directions, and this
5 became a real barrier or problem when it came
6 to being able to deliver appropriate dosing and
7 be able to deliver consistent dosing.

8 Q. When she says "manipulation" here, what does
9 she mean by that?

10 A. Really, any kind of effort by a patient, family
11 or a pharmacy to come up with the final product
12 that was being delivered to the child.

13 Q. Let's take a look, please, at PTX 146. What is
14 this reference?

15 A. This is a review by Richey and colleagues in
16 BMC Pediatrics that looked at the practices in
17 pediatric pharmacology to develop oral
18 formulations using different types of
19 manipulations and highlighted the fact that,
20 for the most part, there were no good
21 evidence-based guidelines. There were a few
22 studies demonstrating what was the best way to
23 formulate these drugs out in the field.

24 Q. So can we take a look, please, at Bates ending
25 in 8080 in the middle of the right-hand

1 paragraph there. What does Dr. Richey say
2 here?

3 A. One of the issues they identified, which we
4 certainly saw, was that manipulations were
5 time-consuming and also had the risk of
6 inaccuracy and stability, and we would
7 certainly get calls from parents saying the
8 medication is out and the pharmacy can't make
9 it. They said come back in three days. They
10 don't have the manpower, they don't have the
11 materials, leading to gaps in care and children
12 missing to doses of important medication
13 because of these manipulation issues.

14 Q. Let's take a look at PTX 082. What does this
15 reference?

16 A. This is Rippley's paper looking at the
17 pharmacokinetics or pharmacology of oral
18 enalapril suspensions for use in children.

19 Q. Who is or are the authors?

20 A. These are investigators working for Merck, and
21 Merck at the time had the brand Vasotec.

22 Q. If we could look, please, at Bates ending in
23 8369. How long were the Merck compounded
24 solutions of enalapril stable for?

25 A. So the data Richey and her colleagues presented

1 for Merck showed that the stability of the
2 products they could come up with was four
3 weeks.

4 Q. Does the fact that the manufacturer for the
5 tablet, Merck, had a recommended compounding
6 method change your opinion that there's a
7 long-felt need for a liquid dosage form of
8 enalapril?

9 A. No, because these are instructions on how to do
10 it. That doesn't really alter the fact that
11 the problems lie in the doing it, having
12 parents do it, having local pharmacies do it,
13 having folks at a rushed, busy pharmacy trying
14 to put something together. Just having the
15 instructions doesn't really meet the need and
16 doesn't really solve significant problems in
17 our patients despite these instructions being
18 in the literature.

19 Q. So you've heard the testimony regarding the
20 Epaned kit; correct?

21 A. Yes.

22 Q. What was your experience with the Epaned kit?

23 A. Well, the kit was definitely an improvement
24 over this extemporaneous compounding. In fact,
25 we stopped asking parents or asking local

1 pharmacies to come up with liquid enalapril and
2 moved strictly to the Epaned kit when it became
3 available.

4 Q. Are products that require reconstitution still
5 a problem?

6 A. Yes, because it still opens the window for
7 significant error and human error. There's a
8 lot of steps involved in reconstituting
9 something, even by a licensed pharmacist.

10 Q. Can we take a look please at DTX 1073. What is
11 this document? The one that says dosage forms
12 and strengths on the top right?

13 A. Yes, so this is the label for the Epaned kit.

14 Q. And please take a look at section 2.4 on page
15 four, please what was required to reconstitute
16 the kit?

17 A. Only 13 steps. So a busy pharmacy tech or
18 pharmacist would have to bang the bottle five
19 times, measure this out, decant this, add that
20 to come up with the final suspension so when
21 the parent got it and it was labeled properly
22 with expiration in 60 days it looked good. But
23 we certainly had concerns about the accuracy of
24 what was being delivered and we certainly have
25 examples where patients would have blood

1 pressure values that raised a concern that
2 perhaps the suspension was not delivering what
3 we had hoped it would deliver.

4 Q. Could a patient take an Epaned kit for more
5 than 60 days?

6 A. We would never allow that. It was only labeled
7 as stable for 60 days. The pharmacist would
8 write discard after and list the date. So if a
9 parent would ever raise that question we would
10 always say discard and you need to get a new
11 prescription. In fact in most cases the
12 pharmacist would only dispense enough for 60
13 days so that's definitely not happening.

14 Q. You previously stated that inaccurate dosing is
15 a concern for you. Why is this particularly a
16 problem in the pediatric population?

17 A. It's really a range of errors, it's really how
18 even small inaccuracies can have profound
19 clinical results in children. For example, a
20 .2-milligram difference is a very small
21 difference if you're an adult taking a
22 2-milligram tablet. That's a two percent
23 difference unlikely to make a significant
24 change in the blood pressure than expected. A
25 .2-milligram, very small error in a child

1 getting a 1-milligram tablet would be a
2 20 percent error, and a 20 percent error could
3 lead to very low blood pressure with all the
4 problems that that can result in like passing
5 out, falling over, under perfusion of important
6 body organs, versus giving too little in which
7 case the blood pressure would be too high
8 leading to some of the clinical consequences of
9 hypertension. So the range for error in
10 children is so much smaller. That's why we
11 have pediatricians and we dose things by body
12 weight to minimize those kinds of things.

13 Q. So let's take a look at slide PDX 209. Is
14 there a commercial product on the market now
15 for a liquid enalapril?

16 A. Yes, that's Epaned ready to use.

17 Q. So once Epaned ready to use was available did
18 you continue to prescribe kits to your
19 patients?

20 A. We could but our pharmacy refused to stock it
21 and we were informed by our hospital pharmacy
22 and therapeutic committee that we were not to
23 use the kit any longer. The only thing we
24 could prescribe because of safety
25 considerations was ready to use. In fact, we

1 can't get the kit in our region.

2 Q. So from a clinical perspective how does Alkem's
3 formulation compare to Epaned?

4 A. They're basically the same thing. They
5 basically deliver enalapril in a stable fashion
6 and reliable way because it's produced by the
7 company so we don't go through any
8 manipulations or compounding and it has a long
9 shelf life of over 12 months. In our view it's
10 the same thing and in fact I wouldn't be
11 surprised if pharmacists if they have that on
12 the shelf would substitute that for Epaned
13 because they would see it as delivering the
14 same medication.

15 THE COURT: Did he just say that the
16 patented product is the same as the accused
17 product?

18 MS. HANSON: From a clinical
19 perspective he would expect the pharmacy to
20 interchange them.

21 THE COURT: Okay. I didn't hear an
22 objection so go ahead.

23 BY MS. HANSON:

24 Q. Could we please take a look at slide PDX 209.
25 What is the major advantage here?

1 A. It really is the stability, that long shelf
2 life.

3 THE COURT: It's 210 by the way, not
4 209.

5 MS. HANSON: Thank you, Your Honor.

6 THE WITNESS: So having a product
7 that has a shelf life of 12 months or more
8 means that more medication can be dispensed to
9 the family, there's less trips to the pharmacy
10 and therefore less breaks in the care.

11 BY MS. HANSON:

12 Q. Let's take a look, please, at slide 211. Did
13 you find an unmet need in this case prior to
14 the invention in 2016?

15 A. Yes, as of March 2016 there was still a need
16 for a stable liquid enalapril formulation
17 without the need for reconstitution or other
18 manipulation and I would highlight stable
19 meaning stable for a long period of time,
20 12 months or longer.

21 Q. So in your opinion does the claimed invention
22 meet that need?

23 A. Yes, the claimed invention and Alkem's ANDA
24 product both meet this long-felt need.

25 MS. HANSON: Thank you. No further

1 questions, Your Honor.

2 THE COURT: Cross.

3 MR. KRATZ: Thank you, Your Honor.

4 CROSS-EXAMINATION

5 BY MR. KRATZ:

6 Q. Good afternoon, Dr. Mahan. So Alkem's product
7 is not on the market; right?

8 A. That's my understanding.

9 Q. So it's not meeting any need until it is
10 allowed to be on the market, would you agree?

11 A. Correct.

12 Q. And you're here today in fact supporting the
13 side that's trying to keep it off the market,
14 yes?

15 A. I'm here talking about the.

16 THE COURT: It's a little
17 argumentative. Everyone knows why he's here.
18 He said he's offering an opinion.

19 BY MR. KRATZ:

20 Q. Part of the opinion -- well okay. But Alkem is
21 not meeting the long-felt need, Alkem's product
22 is not meeting the long-felt need presently; do
23 you agree?

24 A. If it's not available to patients right now it
25 is not meeting the need patients have right

1 now.

2 Q. Okay. You also said the other thing that met
3 the long-felt need were the claimed inventions;
4 correct?

5 A. Correct.

6 Q. Are you aware of any product on the market
7 today or ever that practices the actual claimed
8 inventions in this case?

9 A. No.

10 Q. And the way I wanted to make that clear, you
11 understand, and I want to make it clear, that
12 the Epaned oral solution, their product, their
13 being Azurity, doesn't practice these
14 inventions that we're here about in this case.
15 Do you understand that?

16 A. That's my understanding, yes.

17 THE COURT: Could you excuse me for a
18 second. Go ahead. Sorry.

19 BY MR. KRATZ:

20 Q. I believe on direct you testified what the
21 essence or your understanding of what the
22 patented invention is; correct?

23 A. The claimed invention.

24 Q. The claimed invention?

25 A. Yes.

1 Q. And that's delivering a certain amount of
2 enalapril with a formulation having a certain
3 amount of stability?

4 A. Yes.

5 Q. Did I miss something about that? I don't want
6 to restrict you.

7 A. No.

8 Q. Okay. Did you look at what the unique features
9 of the claimed invention were as against other
10 parts of the claims of the patent, for example?

11 A. Well, as a practicing physician and a
12 clinician, I really am not a formulator, so I
13 really defer to my colleague, Dr. Little, for
14 all the issues around the specifics in the
15 recipes and the formulations.

16 Q. Yes. I understand that. And that's why when
17 you testified from the clinical standpoint,
18 it's the same thing as the Azurity product --
19 it's not the claimed invention -- the Azurity
20 product -- and what appears to be Alkem's
21 product, clinically they'd be the same; right?

22 A. I believe that practicing physicians and
23 pharmacists would look at these and say they
24 both deliver a stable amount of enalapril in a
25 predictable fashion and have a long shelf life,

1 so I think basically they would see them as the
2 same.

3 Q. But from an analysis of the patent and the
4 patented features of what is the difference
5 between these two products, that's not any of
6 your concern; is that correct?

7 A. I really defer to my colleague, Dr. Little.

8 Q. So in determining what satisfies the long-felt
9 need, it's -- for you, you're just looking at
10 these kids that have the high blood pressure
11 and they need to be treated, which I fully
12 understand. We fully understand that as well.
13 But in terms of what makes the patented
14 features --

15 THE COURT: He's not qualified or
16 offered to opine about --

17 MR. KRATZ: That's my point.

18 THE COURT: -- patent infringement
19 issues.

20 MR. KRATZ: It's not infringement.
21 It's the legal standard is not met based on
22 this witness.

23 THE COURT: I misspoke. The witness
24 is not qualified or offered for the purposes.

25 MR. KRATZ: We agree with that, Your

1 Honor.

2 BY MR. KRATZ:

3 Q. I want to talk about a couple of the exhibits.
4 We're not going through them all, I promise.
5 If you could look at PTX 164, you testified
6 about this on direct and you pointed to the
7 page, the second page of the document where it
8 talked about the shelf life should be stable
9 enough to allow for 18 months of shelf life.
10 Do you see that reference? Do you remember
11 that?

12 A. Yes, yes.

13 Q. That's talking about the API; correct?

14 A. Yes.

15 Q. You understand that to be the active
16 pharmaceutical ingredient?

17 A. Yes,.

18 Q. That's the -- as we're talking about here,
19 that's the powder formulation?

20 A. The medication, yes, the pharmaceutical
21 product, so the idea for that, the goal as this
22 task force set it was that that medication
23 should be stable for at least 18 months.

24 Q. But it's talking about the powder formulation
25 before it's put in suspension --

1 A. Yes.

2 Q. -- because that's all we're dealing with here?

3 A. Yes.

4 Q. Are you aware of any issue concerning the
5 stability of the powder formulation in this
6 case?

7 A. No.

8 Q. Okay. But you did talk about stability of the
9 suspension and the next exhibit I wanted to
10 talk about is 82, PTX 82. And you testified
11 about this on direct?

12 A. Yes.

13 Q. Do you agree with the information that's
14 contained in this article?

15 A. Well, it's a peer-reviewed article done by
16 credible investigators that worked for Merck at
17 the time and no reason to not believe the
18 accuracy of their findings.

19 Q. Okay. And they said this is the article that
20 talked about the suspension stability. That's
21 what I wanted to ask you about, suspension
22 stability, and they said, as you pointed out on
23 direct, it's four weeks?

24 A. The products and formulations that they worked
25 up in this lab study, they were stable for four

1 weeks, yes.

2 Q. That's a good point. They're just talking
3 about their suspension they made for the
4 article --

5 A. Correct.

6 Q. -- and it's good for four weeks, but they did
7 say that was acceptable suspension stability.
8 It's in the article; right?

9 A. I'm sure it's their opinion. They stated it.
10 My sense is since pharmacies were using this in
11 the 1990s, this was one of the reasons why they
12 were telling families this is only good for
13 four weeks and you need to come back in four
14 weeks, because this was the most commonly used
15 instructions back in the 1990s.

16 Q. Let's go ahead and look at your -- let's talk
17 about that in a minute and let's talk about --
18 go to your demonstrative used on direct, the
19 210, PDX 210. So this is the -- what you used
20 to demonstrate your opinions regarding
21 stability of the different formulations on
22 here?

23 A. Yes.

24 Q. What I want to ask you about is are we really
25 comparing apples to apples here? If I

1 understand it correctly, the powder for
2 reconstitution -- I'll talk mostly about that
3 even though I just went from the suspension
4 article. I really want to focus on powder for
5 reconstitution, and that's the kit; right? Are
6 you with me?

7 A. Okay. Yes.

8 Q. And the 60 days in that lifespan that's
9 graphical in orange starts at a different time
10 than the green bar that's way bigger, but
11 it's -- the starting point is different. Would
12 you agree?

13 A. Yes.

14 Q. And it's geographically different as much as
15 anything because the powder for reconstitution
16 timeline, the clock of the 60 days, doesn't
17 start until, in the kit situation, for those 13
18 steps when the pharmacist puts it together?

19 A. Right.

20 Q. And then it has to be good for 60 days?

21 A. Right.

22 Q. Whereas the claimed invention, we'll call it
23 and we'll call it Alkem's ANDA product, the
24 oral solution, shall we say, that's produced
25 and sold by one of these companies, it has more

1 than 365 days, but it starts in the factory;
2 right?

3 A. Correct.

4 Q. So when the product is made, then the clock
5 starts ticking; right?

6 A. Correct.

7 Q. And then from there it goes to the wholesaler
8 and then it goes to the pharmacist and sits on
9 their shelf and then when it gets filled, it
10 just continues from that point. It's measuring
11 a different period of time, would you agree
12 with that?

13 A. Correct.

14 THE COURT: How does all that help
15 your case?

16 MR. KRATZ: Your Honor, I'd be happy
17 to explain.

18 THE COURT: I just threw you a
19 softball. Don't tell me you'll be happy to
20 explain. Explain it.

21 MR. KRATZ: The kit was perfectly
22 fine, the shelf life. 60 days is all you need
23 because you're talking about how much time you
24 need it as the patient, and it's not that much
25 different when you get the oral solution

1 product which if they are refrigerated is only
2 good for 60 days also. So this is all about
3 keeping a bulk product on the shelf in the
4 pharmacy.

5 THE COURT: The point is the time for
6 this shelf life is really not as big of a
7 difference between 60 and 365?

8 MR. KRATZ: It's not.

9 THE COURT: Okay. Go ahead.

10 BY MR. KRATZ:

11 Q. Okay. You dose this product by weight, at
12 least for kids; right?

13 A. Yes.

14 Q. How do you account for the variants in weight
15 of a child as they grow?

16 A. We see these children frequently. We would
17 typically see a small child with high blood
18 pressure every three months. The family also
19 would have home blood pressure equipment, so
20 they would be calling in blood pressure values.
21 We would be seeing them every three months. If
22 the child has significant weight gain or we're
23 not getting good blood pressure control, we
24 make adjustments of the dose.

25 So having the liquid allows us to make a

1 change, like from 1.6 mls to 1.8 mls, and we
2 can do that without having to get a new
3 prescription from the pharmacy because we can
4 adjust based on the stable, dependable
5 concentration that's present in that
6 ready-to-use medication.

7 Q. So if they're holding a bottle from the kit,
8 back in the day, the kit, and they're holding a
9 bottle and it's good for 60 days, and they've
10 got a bottle and they can dosage out that too,
11 can't they?

12 A. Correct.

13 Q. And just like if they have the bottle from the
14 OS, it's good for 60 days out of the fridge.
15 So you can call it in to the parent?

16 A. Yes.

17 Q. So that's the same?

18 A. Yes.

19 Q. But then you also, if I understand it, you
20 would change the prescription if the weights
21 changed and fluctuated?

22 A. So the practice would be to get six months of
23 medication, a prescription for six months so
24 the family could have three bottles in the
25 fridge, and if we were making an adjustment,

1 they would just get more out of the second
2 bottle, third bottle.

3 Q. Do you know, when you write a prescription for
4 six months, is it all filled at the same time?

5 A. If I write it for six months, yes, it's filled
6 for six months.

7 Q. Formularies don't give you problems with that?

8 A. Not if I write it for six months. If I wrote
9 it for six years, there might be a problem.

10 Q. Okay. So I don't know if you did -- when the
11 kit was approved in 2013, you moved all your
12 patients to that kit?

13 A. Yes.

14 Q. By the kit, I want to make sure we're talking
15 about the same thing. It's at the pharmacy.
16 You mix it?

17 A. Yes.

18 Q. You used it and believed in it; correct?

19 A. We used it. We knew it was better than what we
20 had. We also knew it that it wasn't as good as
21 what would be desired for our patients.

22 Q. Okay. I just want to be precise. You used it
23 and believed in it, though; correct?

24 A. Yes, the best we had.

25 Q. And the kit is a safe and effective oral

1 formulation; right?

2 A. Yes.

3 Q. When the kit came out, the general reaction of
4 those in pediatric nephrology was hallelujah?

5 A. This was an improvement.

6 Q. And the reaction was hallelujah? Those were
7 your words.

8 A. I didn't hear everybody's shouts but yes, we
9 were happy to have a improvement over
10 extemporaneous compounding at pharmacies and by
11 parents.

12 Q. Fair enough. It became the go to formulation
13 for treatment of hypertension in children that
14 required liquid formulation at that point?

15 A. Yes.

16 Q. When you moved away from compounding and to the
17 kit, you did not see any significant adverse
18 effects from the dosing from the kit; correct?

19 A. We did not have any cases where we could say
20 this was made incorrectly. We heard reports of
21 that, stories about it, we had concerns about
22 it but we did not have any situations where we
23 were able to say take liquid from a
24 reconstituted kit and show that it was made
25 incorrectly.

1 Q. And from your perspective the kit did away with
2 problems with compounding for enalapril; right
3 and I'm terrible at pronouncing enalapril.

4 A. Enalapril. It still requires reconstitution
5 and manipulation. It still requires the
6 pharmacist to go through a complicated series
7 of steps to deliver the product that the
8 manufacturer expects, 13 steps in fact, when
9 they take that bottle of powder, take that
10 bottle of liquid and come up with a medication
11 that they put a label on and put in the parents
12 hand.

13 Q. And the mixing, let's talk about the mixing.
14 The mixing of the kit is done by pharmacists;
15 correct?

16 A. Correct.

17 Q. And the reconstitution of the kit is a very
18 routine task for a licensed pharmacist; is that
19 right?

20 A. I would expect so.

21 Q. Of the 13 steps you talked about in direct,
22 five of them were each individual tap that it
23 says in the label?

24 A. I noted that they didn't say tap it 50 times,
25 they didn't say tap it as much as you want,

1 they didn't say tap it once, they say tap it
2 five times.

3 Q. I'm just asking, your counting the 13 steps we
4 talked about, five of those were these taps?

5 A. Each one of those was clearly stipulated as a
6 step that was required by people in a pharmacy
7 to come up with this product.

8 Q. Okay. You've seen no evidence at all in your
9 practice that if there were variations from
10 those instructions that we're talking about
11 that that would result in inaccurate or
12 incorrect dosage of the liquid; correct?

13 A. None that we could attribute to that, yes.

14 Q. Okay. And you didn't have any issues at all
15 with reconstituted oral solution from Epaned
16 kit; correct?

17 A. Correct.

18 Q. And you have not actually seen any evidence of
19 inconsistency in the dissolved active
20 ingredients in the kilt?

21 A. Not with our patients.

22 Q. And in the time that you and your group
23 prescribed the Epaned kit you did not see any
24 instance where the resulting oral liquid
25 formulation was incorrectly dosed in any way?

1 A. Not in our practice.

2 Q. And you're not aware of any instance in
3 anyone's practice anywhere where the kit was
4 not reconstituted in the proper dose?

5 A. Not that I'm aware of.

6 MR. KRATZ: That's all I have.

7 THE COURT: Any redirect?

8 MS. HANSON: Two things. One thing I
9 wanted to clear up. Could we take a look,
10 please, at PTX 164.

11 REDIRECT EXAMINATION

12 BY MS. HANSON:

13 Q. And could we go to Bates ending in 6891. On
14 the bottom right corner could we blow that up.
15 Do you recall Mr. Kratz asking you if this
16 paragraph was with respect to 18-month shelf
17 life of the powder formulation? Do you recall
18 that?

19 A. It's my understanding when developing liquid
20 dosage forms the solubility and the stability
21 of the API are critical for designing an
22 appropriate drug product. I assume that the --
23 what this means is that API should be stable
24 enough to give a liquid formulation that lasts
25 for 18-months. That's what Zajicek and

1 colleagues were saying is the gold standard.
2 The liquid made from the API should last for
3 18 months.

4 MS. HANSON: No further questions,
5 Your Honor.

6 MR. KRATZ: No further questions.

7 THE COURT: Okay, thank you. So the
8 witnesses that are left from the plaintiff's
9 side?

10 MR. KONG: Plaintiffs have Dr. Little
11 who will be rebutting Dr. Constantinides. I
12 assume Your Honor wants a time estimate. We're
13 guessing 2, 2 plus because there's a lot of
14 materials to go through. So we probably can
15 start today. I wanted to take a temperature
16 check with Your Honor and see where you are.
17 It looks like we'll be having witnesses on
18 tomorrow for sure.

19 THE COURT: Little is going to rebut
20 Constantinides; is that right?

21 MR. KONG: Constantinides. I
22 apologize if I'm mispronouncing it.

23 THE COURT: All right. And then are
24 you done with live witnesses?

25 MR. KONG: We are done.

1 understood by a person of skill in the art. Do
2 you recall that?

3 A. Yes.

4 Q. And did apply that same understanding to your
5 validity opinions?

6 A. Yes, I did.

7 Q. And could we pull up PDX 104, please.

8 Dr. Little, did you hear
9 Dr. Constantinides's opinion this morning about
10 his opinion that hydrolysis does not convert
11 enalapril to enalaprilat and that the status of
12 enalapril as a prodrug is irrelevant?

13 A. I did hear that.

14 Q. Do you have a response?

15 A. I do. I disagree. First of all, the prior art
16 that I reviewed in this case, some of which was
17 put forth by Dr. Constantinides, says the
18 opposite. The degradation products they're
19 detecting in the solution with water is
20 enalaprilat, so that means that it would have
21 had to have hydrolyzed in the water. And that
22 also means it can hydrolyze outside of the
23 liver because those tests weren't done in the
24 liver. They were done in a tube. I also have
25 a large amount of experience myself dealing

1 with esters. I work with them all the time. A
2 lot of the materials that we work on, they
3 wouldn't function the way that we want them to
4 if they don't degrade in water. The bond
5 breaking and the understanding of the chemical
6 nature of a hydrolysis event with water and
7 that bond is very well-known, and it does
8 degrade in water outside of the body.

9 Q. Thank you, Doctor. Could we have PDX 314,
10 please.

11 Dr. Little, could you tell us what's on
12 PDX 314, please.

13 A. Sure. This is the legal standard that I
14 utilized in order to examine the definiteness
15 of the claims, specifically in response to the
16 opinions on indefiniteness. I understand that
17 in order to meet the definiteness, the claims
18 must inform a person of ordinary skill of the
19 scope of the invention with reasonable
20 certainty and that's in light of the
21 specification and prosecution history, and the
22 person doing that is the person of ordinary
23 skill in the art.

24 Q. Do you agree with Dr. Constantinides that the
25 term "stable" as used in '621 patent does not

1 THE COURT: If we raise my same
2 question but from a view of a POA, it's still
3 the same thing. I mean, I'm not hearing
4 anything from either side on this issue that's
5 particularly factually -- or based on their
6 very impressive -- all the experts in this case
7 have qualifications. That's helpful. So I'm
8 asking you, is this typically an issue where
9 experts weigh in?

10 MS. DEVINE: Yes.

11 THE COURT: It is?

12 MS. DEVINE: Every time I've seen it.

13 THE COURT: Every time? Seems
14 counterintuitive. Go ahead.

15 MS. DEVINE: We'll move to written
16 description.

17 THE COURT: Go ahead. As much as you
18 can do before 4:00.

19 MS. DEVINE: I keep checking the
20 time.

21 THE COURT: And I won't cut you off.

22 MS. DEVINE: I'll tell you each time
23 I'm going to move subjects.

24 THE COURT: Thank you.

25 BY MS. DEVINE:

1 Q. Can we go to PDX 314, please.

2 Dr. Little, what standards did you apply
3 in forming your opinions on written
4 description?

5 A. So in order for there to be written
6 description, the applicant would need to convey
7 the invention with reasonable clarity to those
8 skilled in the art in the specification. What
9 I'm talking about here is the four corners of
10 the specification. It's internal to the
11 specification that you're making that
12 determination. Examples are not required for
13 this and actual reduction to practice is not
14 required for this.

15 Q. Did you hear Dr. Constantinides's opinion that
16 the patents do not describe formulations
17 containing parabens and having the claimed
18 stability?

19 A. Yes, I heard that opinion.

20 Q. And do you agree with that opinion?

21 A. I don't.

22 Q. Again, we'll go through some portions of the
23 specification. Can we go to PTX 1, which is
24 the '482 patent, at column six, lines 35 to 37.
25 Dr. Little, does the specification describe

1 embodiments of the invention that include
2 parabens?

3 A. Yes. It says that in some embodiments, the
4 preservative is a paraben. And in some
5 embodiments, the preservative is a mixture of
6 parabens.

7 Q. And could we go to column 12, line 34, to
8 column 13, line 7, please.

9 What other information does the
10 specification provide to a person of skill
11 about parabens in the claimed invention?

12 A. It goes on to give further information to a
13 person of ordinary skill in the art. It
14 provides concentrations in milligram per
15 milliliter of each of these, and it also goes
16 on with respect to the weight of all of the
17 other components of the formulation, what
18 weight of the parabens would be with respect to
19 that.

20 Q. And could we go to column 10, line 23 to 32,
21 please.

22 Doctor, Does the specification provide
23 examples of different types of parabens?

24 A. It does. It provides there -- so such as, and
25 it includes a list. So methylparaben

1 ethylparaben, propylparaben, butylparaben, and
2 their salts.

3 Q. And does the specification provide examples of
4 formulations that contain parabens?

5 A. It does.

6 Q. Can we go to Table A1, please.

7 Could you please tell us what examples of
8 paraben formulations are in this table.

9 A. Sure. So I mentioned this yesterday in the
10 testimony, but this is a chart of various
11 formulations, A1 through A6, and A5 has
12 methylparaben sodium, and A6 has methylparaben
13 sodium and propylparaben sodium.

14 Q. And could we go to Table C1 please. Are there
15 examples of paraben formulations in Table C1?

16 A. There are. So examples C1 through C5 contain
17 methylparaben sodium and likewise, C1 through
18 C3 also contain sodium propylparaben.

19 Q. And can we go to column 18, lines 41 to 45,
20 please.

21 What does the specification tell a person
22 of skill about the stability of the invention?

23 A. It tells a person that in regard to stability
24 what the specific standard would be, which is
25 95 percent or greater of the initial enalapril

1 amount and 5 percent weight per weight or less
2 total impurities or related substances at the
3 end of a given storage period.

4 Q. And could we go further down that column,
5 please, to 18, line 64, column 19, line 2.

6 What does the specification tell a person
7 of skill about the length of stability of the
8 invention?

9 A. It provides the time periods by which the
10 formulations described herein are stable, and
11 it talks about between 1 and 30 months with a
12 number of intervals, including 12 months,
13 18 months, and 24 months.

14 Q. Doctor, with all that information in the
15 specification, in your opinion, does the
16 specification convey to a person of skill the
17 invention of the asserted claims with
18 reasonable clarity?

19 A. Yes.

20 Q. All right. I'm going to switch subjects, and I
21 may --

22 THE COURT: What's the next subject?

23 MS. DEVINE: Enablement.

24 THE COURT: How long are you going to
25 be on that?

1 MS. DEVINE: That one is going to
2 take a little bit longer.

3 THE COURT: How much longer? I won't
4 hold you to it. Ballpark.

5 MS. DEVINE: I want to say like 15,
6 20 minutes.

7 THE COURT: Let's do that, and we'll
8 call it a day.

9 MS. DEVINE: All right.

10 BY MS. DEVINE:

11 Q. Could we go to PDX 317.

12 Doctor, what legal standard did you apply
13 in forming your opinions regarding enablement?

14 A. Right, so I put them on the slide here. The
15 patent provides sufficient information to allow
16 a person of ordinary skill in the art to
17 practice the claims without undue
18 experimentation, also recognizing that some
19 experimentation is not the same as undue
20 experimentation. Also, the post-filing
21 prosecution history beyond what's in the
22 specification can serve as evidence of
23 enablement.

24 Q. Do you agree with Dr. Constantinides's opinion
25 that the patent -- that the patents do not

1 enable to person of skill to make and use
2 formulations containing a paraben or a mixture
3 of parabens having the claimed stability?

4 A. No.

5 Q. In your opinion, does the specification allow a
6 person of skill to make such a formulation?

7 A. Yes.

8 Q. Does a person of skill in the art need examples
9 of formulations with a paraben or a mixture of
10 parabens that includes a full year of stability
11 data to practice the claims?

12 A. No, they would not.

13 Q. And in your opinion, is assessing preservative
14 function in a formulation a routine activity
15 for a person of skill?

16 A. Yes, it would be.

17 Q. Are there inventor declarations in the
18 prosecution history that confirm your opinion?

19 A. Yes, there are.

20 Q. And are you referring to the three declarations
21 by Dr. Mosher that we heard Dr. Constantinides
22 talk about this morning?

23 A. Yes. There's three declarations, yes.

24 Q. And do those declarations show that Dr. Mosher
25 was able to make formulations disclosed in the

1 invention and get stability data for them?

2 A. Yes, a number of them.

3 Q. And how does that support your opinion?

4 A. What it does is it supports the idea that
5 somebody would be able to take different
6 materials, combine them together into a
7 formulation, particularly the type that are
8 discussed within the context of the
9 specification of the patent in suit. They
10 would then be able to perform the necessary
11 experimentation to be able to determine a
12 stability profile.

13 Q. And did you hear Dr. Constantinides point out
14 that none of the formulations that Dr. Mosher
15 made in those declarations contained parabens?

16 A. Yes, I did.

17 Q. Do you agree with that fact?

18 A. In my recollection the -- the formulations in
19 the prosecution history were sodium benzoate
20 formulations.

21 Q. How can you say that Dr. Mosher being able to
22 make sodium benzoate formulations without undue
23 experimentation supports your opinion that a
24 person of skill could make paraben
25 formulations?

1 A. Parabens are something -- for instance, Your
2 Honor heard a bunch of testimony about parabens
3 in the obviousness analysis and looking at the
4 prior art and seeing the paraben formulations.
5 Some of those paraben formulations had one
6 paraben in them, some of them had a mixture of
7 parabens in them, and those references were
8 just taken as, you know, you would know how to
9 put it into the formulation and you would know
10 how to use it to make it. Now you have -- now
11 you have the specification itself, which is the
12 context of these long-term stable formulations,
13 you have specific parabens that are called out
14 concentrations such that you're seeing even
15 more information than someone would have in an
16 obviousness analysis. So these additional
17 declarations show that even further variations
18 are capable of being made. They're able to be
19 tested for stability, so there's no reason to
20 believe that somebody would have undue
21 experimentation in making these embodiments
22 which are described in the specification and
23 testing them for stability.

24 Q. Thank you, Doctor.

25 MS. DEVINE: Your Honor, I spared you

C E R T I F I C A T E

STATE OF DELAWARE)
) ss:
COUNTY OF NEW CASTLE)

I, Deanna L. Warner, a Certified
Shorthand Reporter, do hereby certify that as
such Certified Shorthand Reporter, I was
present at and reported in Stenotype shorthand
the above and foregoing proceedings in Case
Number 19-2100-MSG, *AZURITY PHARMACEUTICALS,*
INC. vs. ALKEM LABORATORIES, LTD., heard on
August 17, 2022.

I further certify that a transcript of
my shorthand notes was typed and that the
foregoing transcript, consisting of 237
typewritten pages, is a true copy of said **BENCH**
TRIAL.

SIGNED, OFFICIALLY SEALED, and FILED
with the Clerk of the District Court, NEW
CASTLE County, Delaware, this 26th day of
August, 2022.


Deanna L. Warner, CSR, #1687
Speedbudget Enterprises, LLC

IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC.,)
)
-----Plaintiff,)
) Case No.
vs.) 19-2100-MSG
)
ALKEM LABORATORIES LTD.,)
) Volume III
-----Defendant.)

TRANSCRIPT OF BENCH TRIAL

BENCH TRIAL had before the Honorable
Mitchell S. Goldberg, U.S.D.C.J., in Courtroom
4B on the 18th of August, 2022.

APPEARANCES

MORRIS NICHOLS ARSHT & TUNNELL LLP
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-and-

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TINA HANSON, ESQ.
EVAN SUMNER, ESQ.
JODY KAROL, ESQ.
JESSICA RAMSEY, ESQ.

Counsel for Plaintiff

1 corroborating someone else's position.

2 MS. DEVINE: What he's telling you is
3 that as a formulator, analytical chemists
4 contribute to these types of formulations.

5 THE COURT: That's not what he just
6 said. He's now telling me that evidence is
7 being corroborated. I mean, this is my --
8 that's my job.

9 MS. DEVINE: I understand.

10 THE COURT: Let's move on.

11 MS. DEVINE: Okay.

12 THE COURT: And your job to -- to
13 make that argument. You don't have to call an
14 expert to button down every single, you know,
15 proposition that you're making. I don't think
16 he's qualified to tell me who corroborated
17 what. So let's move on.

18 MS. DEVINE: I understand, Your
19 Honor. The only point I was trying to make is
20 that --

21 THE COURT: I understand your point.
22 Move on.

23 MS. DEVINE: Okay. Thank you.

24 BY MS. DEVINE:

25 Q. Let's move on to obviousness. Dr. Little, do

1 you agree with Dr. Constantinides' opinions
2 that we heard yesterday?

3 A. I did hear the obviousness opinions, yes.

4 Q. And do you agree with them?

5 A. I do not.

6 MS. DEVINE: Could we turn to PDX
7 302, please.

8 BY MS. DEVINE:

9 Q. Could you tell us in general what you don't
10 agree with?

11 A. Right. So what I don't agree with is, first of
12 all, the way that the analysis was done. In my
13 opinion, from reviewing the reports and from
14 hearing the -- the testimony, what was done was
15 the individual claim elements were looked at
16 first. That was the starting point.

17 And then a search was done in order to
18 identify the specific pieces, and those
19 specific pieces were found in the prior art,
20 but they were not identified together.

21 So the invention as a whole was not
22 looked at, only the individual parts. That, to
23 me, is something that I understand is not
24 proper in an analysis, which is called
25 hindsight. Looking at the -- looking at the

1 prior art through the lens of the invention is
2 what I believe was done here.

3 Also, I did not see a motivation to
4 combine those references. None of those
5 references were about a liquid ready-to-use
6 formulation, and I didn't hear any testimony
7 about why you would combine the individual
8 pieces together.

9 Also, if you have a routine optimization
10 that is being discussed, that would require
11 motivation to optimize it. It wouldn't be just
12 that somebody would try all possible kinds of
13 optimization in order to get to potentially any
14 possible outcome. There would need to be a
15 motivation that is put forth specifically for
16 that invention.

17 Q. Okay. Let's talk about some of the references
18 we heard about yesterday.

19 MS. DEVINE: Can we go to PDX 311,
20 please.

21 And, Your Honor, this is the one that I
22 noticed a typographical error. And this is the
23 correct one on the screen, that bottom blue box
24 had an -- had an extra line in it.

25 THE COURT: Got it.

1 BY MS. DEVINE:

2 Q. Okay. You discussed this demonstrative on
3 Tuesday with this time line. Could you just
4 very briefly tell us how the references that we
5 heard about yesterday fit into that time line?

6 A. Sure. So if Your Honor can recall the slide,
7 everything from the 2013 time point backwards
8 is a prior art reference that talks about
9 compounded formulations. For instance, taking
10 a tablet and crushing it up. And that's sort
11 of the goal of these references, that's what
12 these references are talking about.

13 In 2013 you have two references that talk
14 about essentially a kit, which you would mix
15 one thing together with another. None of these
16 references are talking about a ready-to-use
17 liquid formulation.

18 Q. Do you agree with Dr. Constantinides that a
19 person of skill could have created a long-term
20 stable enalapril liquid formulation through
21 routine optimization in a matter of days prior
22 to the invention?

23 THE COURT: Could you restate that
24 question again.

25 BY MS. DEVINE:

1 Q. Sure. Do you agree with Dr. Constantinides
2 that a person of skill in the art could have
3 created a long-term stable enalapril
4 formulation just using routine optimization in
5 a matter of days prior to the invention?

6 A. I don't.

7 Q. And what about this time line tells you that?

8 A. Right. So, first of all, I disagree with that
9 from my own experience and what I understand
10 about the field.

11 But if it were the case that someone
12 could optimize this within a matter of days,
13 what I understand the testimony to be here is
14 that references like Nahata are providing the
15 motivation. That's in 1998. And then Allen is
16 discussing formulations in 1998 that are being
17 used in order to say that someone could get
18 these formulations prepared.

19 If it could be optimized in a matter of
20 days, why are we talking about 30 years,
21 essentially, before we get to the invention,
22 before that happens? That doesn't make sense
23 in the time line.

24 The other thing that you will notice is
25 that in the -- in the middle of this, around

1 2013, the solution to the problem that you have
2 that I understand was motivating in 1998 was
3 not a ready-to-use liquid formulation, it's a
4 kit formulation.

5 And what's important to understand about
6 that is that that solution is stable long term
7 only in a dry powder, so it's not stable in the
8 context of a liquid formulation, being
9 surrounded by water that can degrade it.

10 So to me that doesn't make sense, given
11 what we see as an actual time line in this
12 case.

13 MS. DEVINE: Could we move to PDX
14 304, please.

15 BY MS. DEVINE:

16 Q. Dr. Little, did you hear the question asked
17 this week: Does the prior art teach how to
18 create a 12-month stable liquid form of
19 enalapril.

20 Did you hear that question?

21 A. I did.

22 Q. And do you have an answer to that question?

23 A. I do. And -- and this was something Your Honor
24 identified when asking these questions as to
25 these prior art references teaching how this

1 would lead to an invention like this.

2 And the analogy that I heard you use was
3 bread crumbs. That you understand that there
4 would be enough breed crumbs lying around. But
5 when you look at the analysis here and you see
6 what bread crumbs are here, what you will see
7 is that in order to get to -- remember, what
8 you're getting to is a long-term ready-to-use
9 liquid formulation.

10 But none of the breed crumbs lead up to
11 the point where you would go past a kit
12 formulation that's dry. So all your bread
13 crumbs are prior to this with no long-term
14 stability data in the prior art at all.

15 Then you have nothing to reflect the
16 motivation to use the particular pH that's used
17 in the asserted claims. The pH in all the
18 formulations that are relied upon in order to
19 look at stability are at various pHs. They're
20 not just at this pH 3.3 that is being
21 discussed. So you have bread crumbs going in
22 different directions that a POSA would follow.

23 Then you have teaching away from, in the
24 prior art, the use of a preservative, and
25 particularly the parabens, in the context of

1 formulations for children. That's in the prior
2 art.

3 So that bread crumb trail actually leads
4 you in the opposite direction that the
5 invention would come.

6 And then, finally, as just yet another
7 example, there is mannitol that's discussed as
8 an excipient in these prior art formulations
9 that's used, and this is important, as a
10 stabilizing agent.

11 But in the inventions, mannitol is not
12 required. And, in fact, in one of the
13 dependent claims, it says that it specifically
14 isn't added.

15 So if the prior art has a bread trail
16 crumb that says you need to add mannitol,
17 you're going in the opposite direction of the
18 invention.

19 So in my opinion, there aren't bread
20 crumbs that are actually leading to the
21 invention. In fact, if anything, they're
22 leading away from it.

23 Q. Thank you, Doctor.

24 Let's walk through some of these prior
25 art references for a little bit. First let's

1 talk about the Epaned Kit label and the '747
2 patent. Those are DTX 1 -- 1073 and PTX 85,
3 respectively.

4 Doctor, do you agree that both of those
5 discuss a powder formulation of enalapril that
6 can be mixed with a liquid to form a liquid
7 medicine?

8 A. Yes. These are discussing powder formulations
9 that are dry and they're stored dry, and then
10 the liquid is added. And then they have a
11 short-term stability after that.

12 Q. And you reviewed the prosecution history of
13 these patents; correct?

14 A. Yes.

15 Q. And -- and did you see that the examiner
16 considered these publications in examining the
17 patent prior to issuing it?

18 A. Yes, the examiner considered these.

19 Q. Is the powder in the Epaned Kit a dry powder
20 blend?

21 A. The powder in the Epaned formulation is a blend
22 of the active pharmaceutical ingredient and
23 several excipients. It's a dry powder blend,
24 yes.

25 Q. Is that the same thing as a granulation?

1 A. It's not.

2 Q. Okay. And the '747 discusses both dry powder
3 blends and granulation; correct?

4 A. Yes.

5 Q. The patent -- the '747 patent and the kit label
6 all discuss this blend of enalapril, mannitol,
7 and silicon dioxide; correct?

8 A. Yes.

9 Q. Okay. What did -- and you just touched on this
10 but go ahead and remind us. What did the '747
11 patent say was the function of that mannitol?

12 A. Right. So the '747 patent, one of the main
13 conclusions of this patent is that when you're
14 making a formulation like this, that they're
15 adding an additional excipient, specifically
16 mannitol here. They talk about silicon dioxide
17 as well.

18 But it's in the context of adding
19 something to stabilize the formulation. And,
20 in fact, there's statements in there that's
21 saying that mixtures of this with mannitol in
22 it were the most stable.

23 Q. Now, do you agree with Dr. Constantinides that
24 a person of skill in the art would have removed
25 mannitol from the kit formulation to make a

1 ready-to-use liquid formulation because the kit
2 contains mannitol as a dry excipient?

3 A. No, I do not agree with that.

4 Q. What is your response to that?

5 A. Well, first of all, mannitol is discussed in
6 the prior art as a stabilizing agent in the
7 context of these formulations. If it's
8 stabilizing the active pharmaceutical
9 ingredient, enalapril, I think that what the
10 prior art is teaching somebody that you would
11 want to use the stabilizing agent, not remove
12 it. That's making the opposite of making
13 something stable.

14 And, in fact, remember, in the context of
15 both of these, the stability limitation is
16 90 percent. We saw this before. The context
17 of the current application we're looking at is
18 95. So it needs to be even more stable long
19 term than what's discussed here. So you
20 wouldn't be removing a stabilizing agent from
21 the formulations.

22 But that's not the only reason. Mannitol
23 is not only a dry powder or a solid excipient.
24 It's used in liquid formulations. And, in
25 fact, if you were remember, the specification

1 of the patent in suit mentions mannitol as a
2 potential sweetener. It's a -- it's a -- it's
3 a sugar alcohol.

4 So it can be used in that context. And
5 it's also known in -- in the prior art to be
6 tonicity agent in solutions and other things.
7 So it's well known to be not just for solid
8 formulations, it can also be used in liquid
9 formulations.

10 Q. In your experience as a formulator, have you
11 understood mannitol to be useful in liquid
12 formulations?

13 A. Yes.

14 MS. DEVINE: Let's pull up the '747
15 patent, which is DTX 1073. And let's go to
16 column 11, lines 7 to 12, and column 13, lines
17 29 to 33.

18 I think we have the wrong document on the
19 other side. Next one. I'll ask you the
20 questions without it on the screen. It's fine.

21 MR. KRATZ: I'm sorry, I don't
22 have -- I thought it was going to show up.
23 I've got two different pages or two different
24 columns.

25 MS. DEVINE: Let me just check

1 briefly.

2 THE COURT: Which number?

3 MS. DEVINE: We're looking at the
4 '747 patent which is one of the pieces of prior
5 art.

6 BY MS. DEVINE:

7 Q. Dr. Little, the '747 patent states that the
8 longest stability of the liquid that it
9 discusses is 36 weeks, while the longest
10 stability of the powder is 36 months.

11 Do you see that?

12 A. Yes.

13 Q. Why is the powder in a product like this, a kit
14 product, stable for so long?

15 A. Well, there's no water in it. So it's
16 specifically made to be dry and kept separate
17 from the liquid.

18 Q. And why would a kit be designed like that by a
19 formulator?

20 A. Because -- because it would be known by the
21 formulator, who would be a person of ordinary
22 skill in the art, that when you would put it
23 into water, you would expect there to be more
24 reactions. So it would be very common, not
25 just for this drugs but for other drugs,

1 that -- to make this assumption that it would
2 be more stable in a dry powder form.

3 Q. And when you make a kit, is the expectation
4 that it's the powder that's going to sit on the
5 shelf for a longer period of time?

6 A. Yes.

7 Q. Did you hear Dr. Mahan testify about the steps
8 required to make and prepare a liquid product
9 using the kit and -- and the 60-day shelf life?

10 A. Yes.

11 Q. And is that consistent with your analysis of
12 this being a kit product where the powder is
13 designed to stay on the shelf?

14 A. Yes.

15 MS. DEVINE: Let's look at another
16 part of the '747 patent. Could we go to column
17 13, lines 7 to 10.

18 BY MS. DEVINE:

19 Q. I think you mentioned this earlier. The '747
20 patent has a stability definition of
21 90 percent; right?

22 A. Yes.

23 Q. Okay. So that's lower than the patents in
24 suit?

25 A. Yes. The patents in suit have established a

1 higher standard for stability.

2 Q. And as a formulator reading that, what does
3 that tell you about the amount of stability
4 that was achieved in the '747 patent?

5 A. Well, what it -- what it tells you is the
6 target for this is 90 percent. And, in fact,
7 in -- in many of the prior art references that
8 we looked at, it's 90 percent. So it's a lower
9 standard.

10 To go from these things, which are not
11 long-term stable formulations, to liquid
12 formulations that would be long term, and then
13 increase the mark for stability is something
14 that would be counterintuitive.

15 Because when you put this in for
16 long-term liquid, you would expect it to be
17 less stable, not more stable than a powder
18 formulation.

19 Q. So in a scenario like this, where after decades
20 of a solid pill formulation is on the market,
21 and then a kit that contains a dry powder blend
22 becomes available, as a person of skill, would
23 you conclude that a liquid formulation would be
24 easy to optimize?

25 A. No. I -- I believe that a person of ordinary

1 skill in the art would not believe that that's
2 easy to optimize, especially after -- after
3 30 years of formulations that didn't achieve
4 that stability.

5 Q. Do either the Epaned Kit insert or the '747
6 patent indicate to a person of skill in the
7 art, prior to 2016, that a liquid formulation
8 of enalapril could be made with the stability
9 of the claims?

10 A. No. It doesn't discuss that.

11 Q. Let's move on to another reference we talked
12 ability yesterday, which is Allen. And this is
13 PTX 76.

14 Doctor, did you review the Allen
15 reference?

16 A. I did.

17 Q. Okay. And do you agree with
18 Dr. Constantinides's opinion that the Allen
19 reference renders the formulation of the claims
20 obvious?

21 A. I don't.

22 Q. And, again, in your review of the prosecution
23 history, did you see that the examiner had
24 Allen during prosecution?

25 A. Yes, the examiner considered Allen in the

1 prosecution of the -- the patents in these
2 claims.

3 MS. DEVINE: Could we go to the page
4 Bates ending 170 of this document, please.
5 Could we blow up the enalapril portion, please.
6 BY MS. DEVINE:

7 Q. Now, Allen describes compounded formulations;
8 right?

9 A. Yes.

10 Q. Tablets crush, add liquid; is that right?

11 A. Yes.

12 Q. Okay. And -- and it says label the bottle with
13 an expiration of 60 days; right?

14 A. Yes, it does. It says that in step 8.

15 Q. What does that tell you about the stability of
16 the formulation?

17 A. That they were stable for 60 days, they were
18 not intended to be stable past that, and that
19 they should be discarded or not used after
20 60 days.

21 Q. If you authored an article like this and you
22 believed that your formulation was stable for a
23 longer period of time, would it be rational to
24 make a statement like that?

25 A. If you knew the formulation was stable long

1 term, no, you wouldn't put this in here.

2 MS. DEVINE: Let's go to the first
3 page of the document, please. And let's blow
4 up the -- yes -- no, is that the right spot?
5 Yes, that's the spot I want. Thank you.

6 THE COURT: I forget which witness
7 mentioned the term "novelty," and you may have
8 already covered this. I want to recall. The
9 novelty of the invention of the plaintiff here,
10 is it the stability, the amount of time that
11 it's stable, or is it the combining the powder
12 and the liquid to create the ready to --

13 THE WITNESS: I can explain that. So
14 I would lean more towards your first answer --
15 or your first one, but there's more to it than
16 just that. Because it -- it's not just that
17 it's stable for a year, for 18 months, for two
18 years. It's the fact that it's stable in a
19 liquid to start with.

20 So you -- you start with a liquid. This
21 is not something where you're adding a liquid
22 to a powder after the powder sits on the shelf.
23 You have an invention that started with a
24 liquid and stays in that liquid for the entire
25 stability time and maintains a higher stability

1 standard than what's discussed in the prior
2 art.

3 The reason why this is important is that
4 you have to have all of the various things in
5 the formulation accomplish the particular task
6 you set out for that formulation.

7 THE COURT: That goes to it's a sum
8 of a lot of parts.

9 THE WITNESS: It's the sum of a lot
10 of parts. And it's a number of design
11 criterion that you have to meet with moving
12 parts in it. But none of these things can lead
13 to an instability in water, for this drug, that
14 is susceptible to water degradation for an
15 entire one to two years.

16 MS. DEVINE: May I? May I, Your
17 Honor.

18 THE COURT: Okay.

19 BY MS. DEVINE:

20 Q. So we've blown up this portion of Allen. And,
21 again, I think you already said this, that
22 Allen sets the stability standard as this 90
23 percent, not the 95 percent; right?

24 A. Yes.

25 Q. And -- and how does that inform your evaluation

1 of the 60-day shelf life set in Allen?

2 A. Well, the 60-day shelf life would be for this
3 lower standard, for 90 percent.

4 MS. DEVINE: Could we go to the page
5 Bates ending in 167, please. And let's blow up
6 the first paragraph in the right column,
7 please.

8 BY MS. DEVINE:

9 Q. Now, Allen made three formulations of
10 enalapril; right?

11 A. Yes.

12 Q. Okay. And two of them -- we can probably
13 highlight this in here. This shows us the pH
14 information. Two of those formulations had a
15 pH of 4.7 to 4.8, and one had a pH of 3.9?

16 A. Yes. The OraSweet formulations, both OraSweet
17 and the Ora-Sweet sugar-free, had pHs of 4.7
18 and 4.8. And the cherry syrup formulation in
19 Allen had a pH of 3.9.

20 Q. Did you hear Dr. Constantinides say that the
21 prior art teaches a person of skill in the art
22 that the optimal pH for enalapril is 3?

23 A. Yes.

24 Q. And is -- is that -- and did you hear him say
25 that knowing that a person of skill in the art

1 would aim for 3?

2 A. Yes.

3 Q. Did the authors of Allen aim for 3, would you
4 aim for 3 and end up with a pH of 4.7 to 4.8 or
5 3.9?

6 A. No, you wouldn't.

7 MS. DEVINE: Let's go to the page
8 ending in 168, and let's blow up the -- the
9 stability data. Thank you.

10 And, Your Honor, just for your
11 information, in the table the Enalapril maleate
12 comes after some other drugs and we just
13 scooted it up so we don't have to look at the
14 other stuff.

15 BY MS. DEVINE:

16 Q. All right. Looking at this data, what
17 direction is -- is it trending, what -- well,
18 first tell us what the data is and tell us what
19 the trend is.

20 A. Sure. So if Your Honor can recall, I just
21 mentioned three formulations; there were
22 OraSweet formulations, two of them. The
23 regular OraSweet is on the left and the
24 OraSweet sugar-free formulation is in the
25 middle. The cherry syrup is on the -- on the

1 right.

2 There were two conditions that were
3 performed for stability, both 5 degrees Celsius
4 and 25 degrees Celsius. And the time frame
5 that the formulation was evaluated is on the
6 left-hand side. You see it goes from one to
7 60 days.

8 So in regard to your question about the
9 trending, what you can see is that the
10 formulation on the far left-hand side has gone
11 down to -- it's lost 5 percent stability,
12 almost 5 percent stability, but it's plus or
13 minus .8.

14 What this means is, is this when
15 determining the 95.6, that's an average of a
16 distribution of measurements. So what you will
17 see is that, for instance, some of the
18 measurements that were taken were below
19 95 percent, and some of them were taken were
20 above 99 -- 95 percent.

21 So if you go to the middle column at 5
22 degrees, what you'll see is 97.7 plus or minus
23 1.2. So what that shows you is that that's the
24 average but there were samples that were taken
25 at 60 days that were 96.5 percent, and some

1 that were above the 97.7.

2 And then finally in the cherry syrup
3 formulations, it's 97.0, plus or minus 1.1. So
4 what that means is that there were samples at
5 60 days by this point with the cherry syrup
6 that were 95.9 percent, and then some that were
7 above 97 percent.

8 THE COURT: What -- what exhibit is
9 this again?

10 MS. DEVINE: This is PTX 76. It's
11 Allen. It's the Allen reference.

12 THE COURT: It's Allen. And I'm
13 asking you this, not the witness.

14 MS. DEVINE: Sure.

15 THE COURT: The witness's testimony
16 relates to nonobviousness how?

17 MS. DEVINE: So Dr. Constantinides
18 testified yesterday that a person of skill in
19 the art would look at this data and say I can
20 take this formulation, make a few small tweaks,
21 and get to a long-term stable --

22 THE COURT: And this witness is
23 differentiating these numbers how?

24 MS. DEVINE: So he's -- he's
25 telling -- he's saying this is how I see the

1 data and he's going to tell you what trends he
2 sees in the data and what --

3 THE COURT: I thought he just said
4 it's a downward trend.

5 MS. DEVINE: Oh, I said that but he
6 hasn't said that yet.

7 THE COURT: Someone said it. And the
8 downward trend...

9 MS. DEVINE: Shows degradation;
10 meaning 90 days is where you get.

11 THE COURT: Go ahead.

12 BY MS. DEVINE:

13 Q. So, Doctor, what -- how do you interpret this
14 data and the trends in the data?

15 A. Yeah. So remember, although Allen is really
16 focusing on 90 percent, that's what Allen is
17 looking for. If one were to look at Allen
18 through the lens now of the patent in suit,
19 what you see is that the patent in suit has a
20 95-degree stability limit.

21 So what you can see here in this chart is
22 that samples that are being taken are
23 practically already at the 95 percent mark at
24 60 days, not a year, not 18 months, and most
25 certainly not two years.

1 Q. So you as a person of skill in the art reading
2 the Allen paper, would you conclude from this
3 that you could make a formulation of enalapril
4 that had 12, 18, or 24-month liquid stability?

5 A. No.

6 Q. As a person of skill in the art reading this
7 data, would you conclude that you could just
8 optimize this formulation to make a long-term
9 stable formulation?

10 A. No. And the reason why is, again, this article
11 was published in 1998. So if this was so easy
12 to optimize, I don't know how we're talking
13 about this formulation not being completed in
14 an invention until almost 30 years later.

15 THE COURT: Is there -- it's a yes or
16 no answer.

17 MS. DEVINE: Sure.

18 THE COURT: Is there precedent that
19 you're going to favorably cite that talks about
20 that there should be less weight given to prior
21 art references that are outdated? Is there
22 federal circuit precedent for that proposition.

23 MS. DEVINE: So there's some nuance
24 to the case law. The Courts do address it and
25 do say that it should be given -- it should be

1 considered in deciding what weight it should be
2 given. That's essentially what it says.

3 THE COURT: So it doesn't say
4 outdated prior art should be given -- can be
5 given less weight.

6 MS. DEVINE: So there is -- there --

7 THE COURT: That's just your advocacy
8 point.

9 MS. DEVINE: Well, so there's case
10 law that says if prior art is long before the
11 invention happens, it has less weight. There
12 is -- and -- and we will cite that law in our
13 brief.

14 THE COURT: All right.

15 MS. DEVINE: Okay. Let's move to the
16 next reference, Nahata from yesterday, at PTX
17 81.

18 BY MS. DEVINE:

19 Q. And, Doctor, did you review this Nahata
20 reference in forming your opinions?

21 A. Yes.

22 Q. And this is another 1998 paper; right?

23 A. Yes, Nahata is 1998, from my recollection.
24 It's not on the screen here but that's my
25 recollection.

1 Q. Okay. And do you recall Dr. Constantinides
2 testifying about this paper, and specifically
3 that there is a sentence in here that evidences
4 a motivation to combine the prior art
5 references that he discussed?

6 A. Yes.

7 Q. Okay.

8 MS. DEVINE: Let's pull up that
9 sentence. It's the bottom of the page on the
10 right-hand side and starts "no liquid."

11 BY MS. DEVINE:

12 Q. It states, "No liquid dosage form is
13 commercially available for pediatric patients."

14 Do you recall Dr. Constantinides's
15 testimony about this sentence yesterday?

16 A. Yes.

17 Q. And do you agree with him that this is a
18 motivation to create the formulations of the
19 claims?

20 A. Well, so what I would say is, is that I can see
21 how it would be, as read by a person of
22 ordinary skill in the art, to say that it would
23 be a motivation to make liquid dosage forms.
24 But the specific ones of the invention, what I
25 don't understand, is how this is a motivation

1 to combine prior art references, which I
2 understand is required in this analysis.

3 There's no motivation in this sentence or
4 for that fact what I've read. A particular
5 motivation to specifically combine a number of
6 different references, like -- I can't remember,
7 maybe eight or something different references,
8 that those specific ones would all be combined
9 together in order to piece together the
10 different claim elements.

11 MS. DEVINE: Could we pull up the
12 demonstrative PDX 11 again, please. PDX.

13 BY MS. DEVINE:

14 Q. So where does Nahata in that statement of a
15 lack of a commercial product for children fall
16 on this time line?

17 A. Yeah, it's at the beginning of the time line.
18 So it's 1998, it's on the left-hand side.

19 Q. So following Nahata, and before the invention,
20 was there a commercially available liquid form
21 for children?

22 A. Not for 28, 30 years.

23 Q. Was there a commercially available kit form for
24 children?

25 A. There was in 2013.

1 Q. Let's talk a little bit more about Nahata.

2 Now, Nahata also is in the prosecution history;
3 correct?

4 A. It is, yes.

5 THE COURT: Could you go back to your
6 last slide, please.

7 MS. DEVINE: Sure. That was actually
8 a callout from Nahata.

9 THE COURT: And your point, Doctor,
10 in rebutting this reference, would you repeat
11 it again, please?

12 THE WITNESS: Sure. What my point
13 is, is that my understanding is that there
14 needs to be -- I can see how there can be a
15 discussion about there being a motivation to do
16 it in the first place. That could be argued to
17 be here. Although, this was in 1998.

18 But there's another two things that you
19 need to do in an obviousness analysis; one is
20 to demonstrate that you have a motivation to
21 combine the specific references where the
22 various pieces of the invention were talked
23 about.

24 THE COURT: So let me -- let me ask a
25 question about that. I don't remember who said

1 it but there was discussion about it's safer to
2 have a liquid form for children; right?

3 THE WITNESS: Yes.

4 THE COURT: And -- I lost the thread
5 of my question. Go ahead and finish.

6 THE WITNESS: I could say that it
7 could be the fact -- it could be the case that
8 at this point in time people would understand.
9 I think that's reasonable to believe that
10 people would understand that it would be safer
11 and that it would be more desirable to have a
12 fully liquid formulation. I can see that being
13 here.

14 THE COURT: Right.

15 THE WITNESS: But what I can't see --

16 THE COURT: That was where -- thank
17 you.

18 THE WITNESS: Okay. And my critique,
19 though, is there's two things that are required
20 in an obviousness analysis, especially when
21 there's a number of references. Usually I see
22 several references together, and they're
23 combined. But in this case it's more, seven or
24 eight, I can't remember how many.

25 You have to show reasons to combine those

1 different references together. There's an
2 instruction somewhere to say, ah, I see why you
3 take this one and this one and put these two
4 together for a specific reason.

5 This does not provide that. And there
6 was no other testimony that I saw that provided
7 that motivation to specifically combine
8 inventions together.

9 The other thing that's required is what's
10 called a reasonable expectation of success in
11 achieving the invention, and that I didn't see
12 in the prior art.

13 So my critiques of this are really that I
14 think -- and I just want to make this
15 distinction -- that there can be motivation in
16 the first place to make it, but that's distinct
17 from a motivation to combine references and
18 then a reasonable expectation of success of
19 achieving the invention once you combine those
20 references.

21 MS. DEVINE: What other point --

22 THE COURT: Isn't the motivation that
23 it's safer?

24 THE WITNESS: Right. So you can have
25 a motivation to make it in the first place, so

1 that could be that it's safer. But there also
2 needs to be a specific reason why somebody
3 would have combined the specific references
4 that have been put forth in order to achieve
5 the specific invention we're talking about.
6 Not some other invention, not some other liquid
7 dosage form or powder dosage form or something
8 else.

9 BY MS. DEVINE:

10 Q. Another point, Doctor, when it says no liquid
11 dosage form, could a kit be a liquid dosage
12 form that Nahata is seeking here and that kit
13 came before the invention?

14 A. It could be. So what you could be talking
15 about here is that if you had a powder and then
16 you could take the dosage form, because if you
17 remember in 1998 all you had was compounded
18 formulations, not something that was all this
19 together that you could take just as a liquid.

20 Q. Does this say that it can't be a kit?

21 A. It does not say it can't be a kit, no.

22 Q. Could this be just a motivation to get to kit?

23 A. It could be. It could be.

24 MS. DEVINE: Your Honor, may I
25 continue?

1 THE COURT: Yes.

2 BY MS. DEVINE:

3 Q. Okay. Let's talk about how Nahata defines
4 stability. Let's go to Bates ending 184 and
5 blow up the right column above the results
6 section.

7 How does Nahata define stability?

8 A. Like the other references we've seen, Nahata
9 defines the stability as being greater than or
10 equal to 90 percent of the initial
11 concentration.

12 Q. Let's pull up table one on Nahata that has the
13 information on the formulations. Now these
14 formulations are at pH 7.1, pH 5.1, and pH 4.7;
15 right?

16 A. Yes, so you can get these from the footnotes
17 underneath. Your Honor can see there's little
18 letters. So for instance, under deionized
19 water you see note footnote C and in the middle
20 you see footnote D, and then footnote E, and
21 that's where the pHs are given in this chart.

22 Q. So these are not at pH of 3; right?

23 A. No. They're not at pH 3.

24 Q. So again, does this data indicate that a person
25 of skill would make enalapril formulations at

1 the supposed optimal pH range?

2 A. That's not what they're doing here, no.

3 Q. And again, you don't need to explain to us the
4 data again because it's similarly formatted,
5 but what kind of trend are you seeing in the
6 stability as a pharmaceutical formulator seeing
7 this article?

8 A. Just to orient, the 4 degrees Celsius is at the
9 top and it goes to 91 days. For each of the
10 formulations I can just summarize by saying
11 each of the formulations had samples that were
12 below the 95 percent stability limitation that
13 would be discussed far later in the future in
14 the patents in suit by 91 days. The average of
15 the first one is already below it and then the
16 spread of the data in the next two you have
17 samples that already were registering below the
18 95 percent stability limitation.

19 Q. So as a person of skill in the art if you were
20 reading this before March 2016 would you think
21 that you could make a long term stable liquid
22 enalapril formulation?

23 A. No, not using these. No, you would not.

24 Q. Let's go to the next reference we're going to
25 talk about, which is Sosnowska, which is PTX

1 83. This is another piece of prior art that
2 was discussed yesterday.

3 And again, Doctor, did this reference
4 appear in the prosecution history so it was
5 before the examiner?

6 A. Yes.

7 Q. And Sosnowska only discusses 30 days of
8 stability; right?

9 A. Yes, you can see in the abstract here it only
10 goes to 30 days of stability.

11 Q. And are these compounded formulations?

12 A. They are extemporaneously compounded
13 formulations.

14 Q. So based on that 30-day data could you make a
15 conclusion that it would be stable for a year,
16 for 18-month, for 24 months as a formulator?

17 A. No.

18 Q. Let's turn to the page ending 188, please, and
19 blow up the materials section and the
20 formulation section and highlight it.

21 So it says in this section, "all
22 suspensions contained methyl hydroxybenzoate
23 0.2 percent as a preservative." What's methyl
24 hydroxybenzoate?

25 A. That's methylparaben.

1 Q. And is that the only preservative that's in
2 here?

3 A. Yeah, one preservative, one paraben.

4 Q. So when you looked at this prior art did you
5 see some enalapril formulations with paraben,
6 I'm sorry, some with preservatives and some
7 without?

8 A. In this paper there's preservatives. There are
9 other references that talk about making
10 formulations that don't have preservatives.

11 Q. Let's go back to the page ending in 190, and
12 let's pull up the paragraph that starts the
13 stability on the left-hand side.

14 So how does this paper, PTX 83, define
15 stability?

16 A. It's defined as the retention of not less than
17 90 percent the original concentration.

18 Q. So with all of this prior art that we're
19 looking at defining stability with a 90 percent
20 criterion, what does that tell you as a person
21 of skill in the art about the possibility of
22 getting 95 percent stability for a longer term?

23 A. If you were moving to a formulation that was in
24 a liquid for the entire period of storage,
25 95 percent would be a higher bar than what was

1 discussed in the prior art.

2 Q. So as a person of skill in the art prior to
3 March of 2016 if you were reading this paper
4 would you believe that you could make a
5 formulation of enalapril with the claimed level
6 of stability in liquid?

7 A. No, there's no reason to believe that.

8 Q. Let's go to PTX 78. This is another paper we
9 heard about yesterday, it's Casas. Doctor did
10 you review this paper?

11 A. I did.

12 Q. And did the examiner review this paper in
13 prosecution?

14 A. Yes.

15 Q. Okay. And I can take you to it but do you
16 agree that the enalapril formulation in this
17 article does not contain a preservative?

18 A. Yes, it does not contain a preservative.

19 Q. Okay. Let's go to page 176 and go to the
20 second paragraph there. Could we highlight the
21 sentence, this is a big paragraph, that starts
22 it is advisable.

23 What does this paper for Casas say about
24 including preservatives in pediatric liquid
25 formulations?

1 A. What it says here is that they're advising a
2 person of skill in the art that a preparation
3 should not include a preservative. And they're
4 saying that even including a preservative in
5 very small quantities can cause nonspecific
6 reactions or even allergies, another kind of
7 sensitizations.

8 Q. Does it say anything specific to parabens in
9 this paper?

10 A. Yes, if you continue on it says for example and
11 it specifically calls out parabens and says
12 that these can cause allergic reactions in many
13 other small molecule allergens. And it goes on
14 to say that especially sensitive to these
15 reactions are premature infants, newborns, and
16 toddlers.

17 Q. And we heard from Dr. Mahan that that's exactly
18 the patients who need liquid enalapril;
19 correct?

20 A. Yes.

21 Q. Would -- as a formulator reading this paper,
22 would you be motivated to include a
23 preservative in a liquid form of enalapril?

24 A. No. If you take the advice of what these
25 authors are teaching to a person of ordinary

1 skill in the art, these are bread crumbs that
2 are leading in the other direction.

3 Q. Let's go to the page Bates labeled 179 and blow
4 up the pH determinations.

5 What was the pH of the formulations in
6 Casas?

7 A. There's different formulations here, the
8 Enalapril maleate formulations are going to be
9 four lines up. So it says Enalapril maleate
10 and PEF is pediatric extemporaneous
11 formulations. They have acidic values, 2.55 to
12 2.278.

13 Q. And did you hear Dr. Constantinides testify
14 that he thinks 2.7 and 3 are the same?

15 A. Yes.

16 Q. So this would be a formulation at that magic 3
17 pH; right?

18 A. According to Dr. Constantinides's testimony
19 yes.

20 Q. Let's go to page 181 and blow up the first
21 paragraph.

22 So tell us, and Mr. Smith can highlight
23 something if it makes it easier to read, but
24 tell us what did this paper say about the
25 stability of the formulations?

1 A. Right. The stability studies are discussed in
2 the paragraphs that are called out here. What
3 it says here for enalapril, which is in the
4 bottom column, it says that the drug content
5 was above 95 percent until 50 days and then it
6 says at the bottom after three months, if you
7 take it out now to three months of the study,
8 at this particular pH all three temperatures
9 that were studied the enalapril was decreased
10 by 40 percent. So in other words, at three
11 months you would have only seen 60 percent or
12 less stability.

13 Q. So it talks in days and then it talks in months
14 so 3 months, 90 days; is that right?

15 A. Three months would be approximately 90 days.

16 Q. So at 50 days you'd only lost five percent
17 enalapril, but in the next 40 days you lost
18 another 35 percent of enalapril?

19 A. Right.

20 Q. So if you look at the graph it would fall off
21 the cliff?

22 A. Yeah. So what you have here is you have a
23 period of time that there's no reactions and
24 it's possible in these that once it starts
25 reacting it can start to go faster and this is

1 consistent with idea of something that would
2 degrade by an oxidative means or something that
3 would degrade by catalytic hydrolysis or
4 something like that.

5 Q. Would this teaching in this paper, Casas,
6 motivate you as a person of skill in the art to
7 create a liquid form of enalapril?

8 A. No, this is showing a formulation where you see
9 a very significant drop off in stability at
10 three-months.

11 Q. Let's go to table two of this paper please and
12 blow it up, it's a big table.

13 Doctor, this table has a number of
14 extemporaneously compounded formulations in it;
15 right?

16 A. Yes.

17 Q. And it tells you what the stability of those
18 formulations are?

19 A. On the far right-hand side you can see the
20 number in terms of time and these are in days
21 or months.

22 Q. And how long are they, are they long?

23 A. The longest that you see here is 91 days.

24 Q. Would anything in this table, table two of
25 Casas, indicate to you as a person of skill

1 prior to March of 2016 that a liquid
2 formulation of enalapril could be made with 12,
3 18, 24 months of stability?

4 A. No, this is another set of examples of people
5 showing that it would not only provide 60 days
6 to 91 days of stability once it's hydrated.

7 Q. So let's stop talking about the references and
8 let's talk about whether there was a motivation
9 to combine them and whether a person would have
10 had an expectation of succeeding in doing so.
11 Let's pull up PDX 311, please.

12 As a starting point, do any of the
13 references that Dr. Constantinides talked about
14 discuss long term table enalapril liquid
15 formulations?

16 A. No.

17 Q. And do you agree with him that one would have
18 taken that statement in Nahata that you need a
19 commercial liquid and arrived at the patented
20 invention?

21 A. No, it's my opinion that a person of ordinary
22 skill in the art would not believe that, no.

23 Q. And if you were motivated by that statement in
24 Nahata would you still have that motivation
25 after a kit was available as a commercial

1 formulation?

2 A. No, I think the kit is, again, demonstrating to
3 a person of ordinary skill in the art that
4 after all this time the solution that's put
5 forth is a dry formulation to sit on the shelf.

6 Q. So as a person of ordinary skill in the art
7 prior to 2016, after the 2013 when the kit is
8 available, observing the literature and the
9 history what would the presence of the kit tell
10 you about whether or not you could make a long
11 term stable liquid formulation?

12 A. I think it would tell you that that's the
13 solution that someone came up with to -- to
14 solve this problem. And I think it just
15 exemplifies that the -- and they would also be
16 aware of the molecules. So they're aware of
17 the molecule, that it would be unstable in
18 water, and they would see the solution to the
19 problem is a dry formulation.

20 And that would make a person of skill in
21 the art not believe that it would be easy to
22 make a long-term liquid formulation.

23 Q. Did Dr. Constantinides -- now, we didn't talk
24 about every single reference he talked about.
25 But did he cite anything that -- that included

1 long-term stable liquid formulations of
2 enalapril?

3 A. No.

4 Q. And did he cite anything that instructs or
5 teaches how to make such a formulation?

6 A. No. In fact, as I said, some of the references
7 actually would take you in a difference
8 direction from the claimed inventions.

9 Q. Did he cite anything that indicates that you
10 could just routinely optimize what's already
11 there and get to a long-term stable
12 formulation?

13 A. I -- I don't think I would say that he cited
14 things to say that you could routinely optimize
15 things. I think you can -- I think formulators
16 optimize things. I don't think that
17 formulators don't do that.

18 They can work on optimizing formulations.
19 But, I mean, there's got to be a limitation at
20 some point. I mean, some of the molecules we
21 work with are so unstable, like they're -- some
22 of them are proteins, some of them are, you
23 know, RNA and DNA. They're -- they're -- you
24 know, they're historically known to be
25 extremely unstable.

1 Just because formulators optimize things
2 does not mean that somebody can just optimize
3 everything and come up with a formulation that
4 would be stable in a media that's specifically
5 known to degrade. I'm not saying it's not ever
6 possible, and people come up with inventions.

7 But you, certainly, in this case,
8 wouldn't look at the prior art with what's been
9 shown, with all the short-term stability, and
10 just think it -- that you would just be able to
11 do it.

12 THE COURT: You use the word
13 "optimize" a lot. Can you define it.

14 THE WITNESS: Sure. So I would
15 define optimize as attempting to achieve a
16 particular goal. For instance, if you were to
17 say stability, you can try to manipulate
18 ingredients in order to keep from having the
19 number of reactions that you would potentially
20 have to lead to an unstable formulation.

21 So you can -- you can take things out,
22 you can put things in, you can add stabilizers.
23 You have to be careful because you can't add
24 too many things because if you do then you
25 might mess up the function of something else.

1 So all of those considerations are what
2 we do when we try to make a formulation. And
3 formulators do that. But it doesn't mean you
4 can optimize every formulation.

5 THE COURT: Define optimize for me in
6 one sentence, as you would use it.

7 THE WITNESS: As I would use it, I
8 would say it's trying to achieve all of the
9 necessary functions of a formulation without
10 messing up something else that you need in the
11 formulation, like stability.

12 BY MS. DEVINE:

13 Q. Now, have -- having reviewed all of this, would
14 a person of skill in the art have been
15 motivated, have wanted to, have thought to
16 combine Epaned Kit, the insert, the patent, the
17 '747 patent, the Allen reference, any of these
18 other references, smoosh them all together with
19 the expectation that they were going to end up
20 with a long-term stable enalapril formulation?

21 A. No, I do not think so. And, again, I just
22 think that the reason these references were put
23 forth is that they had pieces of the invention.

24 But there's -- there's no reason that I
25 can see that was put forth specifically to pick

1 the things from each of these, especially when
2 you didn't know that that was going to lead to
3 a long-term stable liquid formulation.

4 Q. So briefly let's -- let's discuss a few things
5 that we saw in Dr. Constantinides's claim
6 charts from yesterday. And we won't read them
7 aloud, but I just want to hear your response to
8 a couple of things.

9 MS. DEVINE: Let's pull up DDX 023,
10 please.

11 BY MS. DEVINE:

12 Q. Now, do you recall seeing this demonstrative
13 from Dr. Constantinides's claim chart
14 yesterday?

15 A. I do.

16 Q. Okay. And the -- the first statement says that
17 "The '747 patent describes stable enalapril
18 powder compositions for reconstitution -- what
19 does "reconstitution" mean?

20 A. It's adding the liquid media, or the -- as we
21 call it, the diluent. But it's the liquid
22 media.

23 Q. Okay.

24 -- into liquid formulations maintaining
25 95 percent or greater of initial enalapril at a

1 storage of at least 18 months."

2 Do you see that?

3 A. Yes.

4 Q. Okay. Is that a correct characterization of
5 the '747 patent?

6 THE COURT: Hold on. If I'm
7 following you right, and I'm looking at this
8 witness's slide 3 of 3, you just covered pretty
9 comprehensively all 11 references of prior art.
10 And he distinguished them. Are you now going
11 to redo that through this chart again?

12 MS. DEVINE: I am -- I am not going
13 to redo it through the chart.

14 THE COURT: Please don't.

15 MS. DEVINE: And we -- I won't. I
16 won't. I just want to point out that --

17 THE COURT: New information. You
18 were very thorough.

19 MS. DEVINE: Sure. I understand.
20 And we -- and we didn't cover all 11 pieces.

21 THE COURT: How many did you cover?

22 MS. DEVINE: I covered one, two,
23 three, four of them.

24 THE COURT: Only four?

25 MS. DEVINE: In detail. I asked

1 broad questions to cover the rest.

2 THE COURT: Okay.

3 MS. DEVINE: It felt longer?

4 THE COURT: Classic patent lawyer
5 answer. And I don't say that disparagingly.
6 You covered all 11.

7 MS. DEVINE: I covered all 11.

8 THE COURT: My impression is that you
9 did. Please don't do it again through this
10 chart.

11 MS. DEVINE: I will not. I -- I just
12 want to make the point here --

13 THE COURT: Go ahead. Ask your
14 question.

15 MS. DEVINE: Sure.

16 BY MS. DEVINE:

17 Q. -- that -- that in that statement is the
18 implication that the liquid formulation had
19 95 percent stability for 18 months?

20 A. Here's how I would say it. To the extent that
21 one might believe that that sentence --
22 sentence means that the '747 patent discloses a
23 liquid formulation that upon reconstitution
24 maintains 95 percent weight per weight or
25 greater for 18 months, that wouldn't be

1 correct. That wouldn't be accurate.

2 It -- it -- it would be if you're talking
3 about the powder being stable for 18 months.

4 Q. Okay. And we discussed on Tuesday the '621
5 patent having this -- consisting essentially of
6 language in it. Do you remember that?

7 A. Yes.

8 Q. And -- and does that mean that it can't have
9 anything in the formulation that affects the
10 basic and novel properties of the invention?

11 Do you remember that?

12 A. That's my understanding, yes.

13 Q. Did Dr. Constantinides identify anything in the
14 prior art that would have motivated a person of
15 skill in the art to remove excipients that
16 would affect the stability of the formulation?

17 A. No. There was one discussion about how
18 somebody would know to remove, for instance,
19 like mannitol. But especially if -- in the
20 '747, if that's discussed in the context of
21 maintaining stability, you wouldn't remove it.

22 MS. DEVINE: Let's pull up
23 Dr. Constantinides's slide DDX 018, please.
24 And I promise I'm not going read it. I just
25 want to reference it.

1 BY MS. DEVINE:

2 Q. He says here that they -- that the prior art
3 would lead a person of skill in the art to
4 18-month stability. And do you recall during
5 his testimony he said this is an achievable
6 goal.

7 Do you remember that?

8 A. Yes.

9 Q. Do you agree that this is an achievable goal?

10 A. Based on everything that we would see, there's
11 no evidence that somebody would think that this
12 is an achievable goal. Again, you have a long
13 time where people are showing not achieving
14 this goal.

15 And then you have a solution to the
16 problem being a dry powder formulation. So I
17 don't think this indicates this is an
18 achievable goal.

19 THE COURT: The goal being stability?

20 THE WITNESS: In a liquid form with
21 all those things in it, that you would achieve
22 stability, yes.

23 THE COURT: I'm sure this has been
24 covered but just remind me, how did the
25 plaintiff in this case, how, tell me how the

1 plaintiff achieved that goal. The stability.

2 THE WITNESS: Okay. What was found
3 is that -- so the road map that the patent
4 gives you is to produce the specific set of
5 combination of things that are in the claim in
6 a liquid format that seems to avoid all of the
7 different reactions that could potentially
8 happen with this drug that would be in a liquid
9 form.

10 THE COURT: Okay.

11 THE WITNESS: As simply as I can say,
12 yes.

13 THE COURT: Okay. Next question.

14 BY MS. DEVINE:

15 Q. We're going to move on to objective indicia of
16 nonobviousness. If we could pull up PDX 312,
17 please.

18 Did you evaluate objective indicia of
19 nonobviousness?

20 A. I did.

21 Q. And do you understand that objective indicia of
22 nonobviousness are facts that existed prior to
23 the invention that indicate that the invention
24 wasn't obvious?

25 A. Yes.

1 Q. And do you understand that those facts have to
2 be linked to the claims?

3 A. Yes, there has to be a nexus, that's correct.

4 Q. Can you tell us what you understand nexus to
5 be?

6 A. Sure. You have objective indicia that you're
7 talking about and you have the claimed
8 invention there's has to be some connection
9 between the two, which is that nexus, so that
10 you can link that objective indicia to the
11 invention.

12 Q. Could we pull up PDX 313, please.

13 In your opinion, what facts show the
14 nonobviousness?

15 A. Sure the unexpected results that we just
16 reviewed that over this long period of time you
17 would achieve not just a stable liquid form but
18 a stable liquid form with and even higher
19 degree of stability than what was specified
20 before. And that's in light of the failure of
21 a lot of others, really, in demonstrating that
22 didn't happen. And then I refer back to
23 Dr. Mahan for the long-felt need that he
24 discussed.

25 Q. So the claims have been discussed extensively

1 and they all require a certain level of
2 stability; right?

3 A. Yes.

4 Q. So they all require that over 12, 18, or
5 24 months, you maintain more than 95 percent of
6 your enalapril in the liquid; right?

7 A. At the specific time point mentioned, yes.

8 Q. Can you please explain to us why based on your
9 review of what came before the invention that
10 was unexpected?

11 A. Sure. I think I've covered it pretty
12 thoroughly, but it's the fact that somebody
13 would be looking in the prior art to see
14 whether or not this would be something that
15 they think -- they have reason to believe that
16 it would be successful and what you're seeing
17 over and over again, after 90 days, after
18 60 days, you're seeing data showing that it's
19 not stable or after three months you're seeing
20 that you've lost 40 percent stability and then
21 you look at the molecule and say yeah, that
22 makes sense, this is an unstable molecule in
23 this liquid. So after all of these data points
24 and after a table we saw in one of the
25 references that shows beyond the seven or eight

1 references that we saw, another seven or eight
2 references, that you see just time and time
3 again you're not seeing that long term
4 stability.

5 Q. And how about failure of others?

6 A. That's what I just discussed too, is that each
7 of those were showing a lack of stability at
8 that time point.

9 MS. DEVINE: Your Honor, with the
10 reservation that I understand Dr. Rabinow is
11 going to discuss the Allen reference and we
12 haven't discussed Dr. Little's rebuttal to that
13 and with the reservation that I would like to
14 recall Dr. Little to rebut that I have no
15 further questions.

16 THE COURT: Okay. Let's take a
17 five-minute break.

18 (A recess was taken, after which the
19 following proceedings were had:)

20 THE COURT: Okay. So cross.

21 MR. KRATZ: Your Honor, before we
22 begin quick housekeeping announcement I guess.
23 In light of the testimony in the trial so far,
24 we've decided not to call Dr. Rabinow for the
25 rebuttal that we intended to do so. So it's my

1 understanding the trial will be concluded after
2 the cross and any redirect here.

3 THE COURT: Okay. Cross-examine.

4 MR. KRATZ: Okay.

5 CROSS-EXAMINATION

6 BY MR. KRATZ:

7 Q. Good morning, Dr. Little.

8 A. Good morning.

9 Q. We talked a couple days ago.

10 A. Yes.

11 Q. I'm just going to ask, actually, just a few
12 questions. I want -- you testified yesterday
13 about the declarations of Dr. Mosher --

14 A. Yes.

15 Q. -- right? Okay.

16 THE COURT: Could you -- could you --
17 so I can follow this, that's in video that I'm
18 going to look at; right?

19 MR. KRATZ: Well, there is video
20 testimony of Dr. Mosher. He's an inventor.
21 The declarations have been talked about
22 throughout the case, and I was going to ask a
23 couple contextual questions.

24 THE COURT: So I can have the
25 context -- and this is probably a reason why I

1 should have watched it, so I can have the
2 context. Give me the backstory so I can follow
3 the context of your questions if you're going
4 to ask about Mosher.

5 MR. KRATZ: I think I can get the
6 backstory with a little bit of question and
7 answer. If I need a little help -- if not, I'm
8 happy to speak, but I think the witness will
9 give us the context in a few short questions.
10 If I'm wrong about that, we'll do it another
11 way.

12 BY MR. KRATZ:

13 Q. Dr. Mosher is one of the inventors named in
14 these two patents; right?

15 A. Correct.

16 Q. And he submitted three declaration over the
17 course of the prosecution of those patents that
18 you reviewed; right?

19 A. Yes, I reviewed three.

20 Q. And those declarations have been talked about.
21 They're in evidence. They provide long-term
22 data of stability that supported the patents
23 that issued, ultimately, as the '482 and '621
24 patents; correct?

25 A. They do discuss stability in them.

1 Q. They actually have the only data that we've
2 ever seen that has stability 12 months or
3 longer in advance of the submission of the
4 issuance of these patents; isn't that right?

5 A. I don't recall that. I do recall there was
6 long-term stability data in those declarations.

7 Q. And at least with respect to those
8 declarations, it went out to 12 months?

9 A. Or longer than 12 months.

10 Q. Fair enough. And we'll talk about what the
11 patents disclose in a minute, but the
12 declarations do disclose data -- at least 12
13 months of stability for the formulations in
14 those declarations; correct?

15 A. That's my recollection, yes.

16 Q. And that went to the Patent Office, and that's
17 one of the reasons why the patents were issued;
18 correct?

19 A. It went to the Patent Office. The details
20 about why the patent was issued, I don't
21 remember.

22 Q. Fair enough. And I think that's the context,
23 but the question I want to explore is that none
24 of the data that the declarations that we're
25 talking about involved formulations that cover

1 the claims that are at issue in this
2 litigation. Do you agree with that?

3 A. What do you mean by that? Sorry.

4 Q. None of the data have parabens; right?

5 A. So yes, so the data in those declarations, the
6 specific data you're talking about, there's not
7 parabens in that data.

8 Q. Right. And the claims that are at issue in the
9 case all require parabens in the formulation;
10 correct?

11 A. They do.

12 Q. Okay. So this data -- and to be clear, this
13 data has a formulation of sodium benzoate as a
14 preservative instead of parabens; correct?

15 A. To my recollection, that's correct.

16 Q. And the Epaned oral solution product that is on
17 the market by Azurity, that's the one that has
18 sodium benzoate as the preservative; correct?

19 A. That formulation has sodium benzoate in it.
20 That's my recollection, yes.

21 Q. And there's no data that goes out to 12 months
22 at all with a formulation that has parabens;
23 correct?

24 A. Sure. And I talked about that in my direct.

25 Q. I understand. I understand. I just want to

1 MR. KRATZ: Yes.

2 BY MR. KRATZ:

3 Q. Does either patent have a disclosure of a
4 formulation that meets all of the asserted
5 claim limitations for any claim that's asserted
6 in this case?

7 A. Right. So as I testified yesterday, the patent
8 includes data on paraben formulations. Those
9 paraben formulations weren't taken out in this
10 particular case to the longer term. Other
11 formulations were. But those formulations
12 weren't taken out to 12 months.

13 Q. So if I understand it, the answer is no?

14 A. Yes, that's correct.

15 Q. Okay.

16 A. The 12-month piece wasn't available for the
17 paraben formulations. It was available for the
18 other formulations in the patent.

19 Q. For, like, the sodium benzoate that Dr. Mosher
20 supplied the declarations in that didn't have
21 parabens and had data for other products;
22 correct?

23 A. I'm sorry. I don't understand your question.

24 THE COURT: Could you give me a
25 second, please.

1 Go ahead.

2 MR. KRATZ: I'm -- I'm withdrawing
3 the unintelligent question I just asked. And
4 we're going to move to a new topic.

5 BY MR. KRATZ:

6 Q. I'm going to ask only about one reference of
7 the prior art, so we're not going back through
8 -- slogging through anything. I'm going to
9 look at the '747 patent.

10 And for context, the first thing I'm
11 going to do is make sure it's in front of you.
12 So it's -- this is DTX 1094. And again, this
13 is already in evidence, but we have lots of
14 copies.

15 THE COURT: Is this a new exhibit?

16 MR. KRATZ: No, this is -- this is --
17 I'll get the context for it, but we have lots
18 of copies.

19 Do you have it?

20 THE WITNESS: Yes.

21 MR. KRATZ: Okay. You can use that
22 or this.

23 THE WITNESS: I can use this one.

24 MR. KRATZ: Okay.

25 BY MR. KRATZ:

1 alone, dry, and therefore more stable.

2 We're -- it's in the environment that it's been
3 put in that is -- is aqueous?

4 A. Again, I think what you're generally saying is
5 right.

6 Q. Okay. So -- and these charts show data out to
7 12 weeks. Do you agree?

8 A. 12 weeks.

9 Q. Right. And this shows refrigerated, which is
10 often in the industry 5 C plus or minus 3?

11 A. Yes.

12 Q. Okay. And the refrigerated column of the first
13 one stays above a hundred, in fact, the entire
14 time of the 12 weeks; correct?

15 A. For 12 weeks, yes.

16 Q. Okay. And the -- the second one, that stays
17 above -- from 0 at 95.86 you're still, by 12,
18 at 95.74 in refrigerated conditions; correct?

19 A. Correct.

20 Q. And -- and do we have any indication that it
21 would not be stable past the 12 weeks?

22 A. Well --

23 Q. I'm -- I'm -- okay.

24 A. Yeah, I just don't -- your question is not how
25 a formulator is thinking. You're not looking

1 at only 12-week data and saying that you're
2 going to project out to two years of stability.
3 It's only 12 weeks of data.

4 And these reactions, as I testified, they
5 can fall off a cliff.

6 Q. That's what I want to ask you about. A
7 formulator isn't waiting two years to see if
8 his stuff is good; right? A formulator has to
9 make projections, doesn't he or she?

10 A. Well -- well, I mean, technically what happens
11 is that you are doing long-term stability
12 studies and you can do accelerated studies --

13 Q. Right.

14 A. -- as well.

15 Q. You can't wait --

16 MS. DEVINE: Can he finish his
17 answer?

18 THE COURT: Go ahead. Finish your
19 answer.

20 THE WITNESS: Sure. But the
21 accelerated studies that you do are out to at
22 least six months before the FDA will even look
23 at them and consider whether or not the data in
24 those studies would warrant the determination
25 that was being made by the data.

1 seen any testimony by anybody about economic
2 factors, like an expert in economics in this,
3 but I am not an expert in economics. All I can
4 testify to is as a formulator.

5 BY MR. KRATZ:

6 Q. I'm just asking if you took that into account
7 at all, and it sounds like the answer is no. I
8 just want to know --

9 A. No.

10 Q. The answer is no?

11 A. That is correct.

12 MR. KRATZ: All right. I have
13 nothing further.

14 THE COURT: Any redirect?

15 MS. DEVINE: I have a few. I won't
16 say I will be brief.

17 REDIRECT EXAMINATION

18 BY MS. DEVINE:

19 Q. So Dr. Little, there was one question that I
20 was kind of confused by the way that it was
21 worded so I just want to make sure this is
22 clear on the record. In your opinion does the
23 patent convey to a person of skill in the art
24 with reasonable clarity the formulation of the
25 asserted claims with parabens, with enalapril,

1 et cetera, et cetera?

2 A. Yes.

3 Q. Okay. And does the patent provide to a person
4 of skill in the art sufficient information to
5 make those formulations with a single paraben
6 without undue experimentation?

7 A. Yes, it does.

8 Q. Okay. And is that for the reasons you
9 discussed on your direct testimony, both of
10 those questions?

11 A. Yeah, it's for the reasons we discussed and
12 it's also.

13 THE COURT: And now he's going to
14 explain it again.

15 MS. DEVINE: I don't need you to
16 explain. I was only looking for a one word
17 answer.

18 THE WITNESS: Yes.

19 THE COURT: You were tieing them
20 together.

21 MS. DEVINE: Yes.

22 BY MS. DEVINE:

23 Q. Can we go to the data in the '747 patent that
24 Mr. Kratz had on the screen. It's example two,
25 Mr. Smith. Column 23, the top two. Perfect.

1 I should look at the screen.

2 Okay. So you said, I believe, on cross,
3 and correct me if I have it wrong, I was
4 scribbling, if data reflects that you're having
5 reactions at accelerated time -- accelerated
6 temperatures, then that indicates a lower
7 likelihood that you're going to have long term
8 refrigerated stability. Did I get that right?

9 A. Yes, in fact if you have reactions at the
10 accelerated condition the FDA now says that you
11 should not assume that you have that and you
12 have to do additional work.

13 Q. So here accelerated would be the higher than
14 refrigerated temperatures; is that right?

15 A. Yes.

16 Q. Okay. So that would be room temperature to
17 25 degrees and 40 degrees?

18 A. Well the condition that the FDA would use is
19 the 25 degrees Celsius and 60 percent relative
20 humidity.

21 Q. And I'm going to ask you a question and I'm
22 only looking for a yes or no. Does the data
23 here in these tables in the room temperature
24 condition indicate that you are having
25 reactions?

1 A. Yes, and the reason why is because the FDA
2 specifically calls out the substantial amount
3 of reaction you would have to be 95 percent,
4 and if you have that before the six-month time
5 point, then now you know that there's something
6 going on. So what this data would show both --
7 in both of the formulations that I was shown is
8 that it's below 95 percent and it's only at
9 12 weeks. So you would certainly have that
10 amount at six months, and that would mean
11 there's something going on.

12 MS. DEVINE: No further questions.

13 THE COURT: Okay.

14 Thank you.

15 Is that -- aside from the testimony, my
16 homework, there's no other testimony; right?

17 MR. KRATZ: That's correct.

18 MS. DEVINE: We have no further
19 witnesses.

20 THE COURT: Okay. So I said
21 yesterday I'd like to -- I mean, I'm happy to
22 get some input on how all -- you know, this
23 will be wrapped up and presented to me.
24 I mean, I -- sort of stream of consciousness
25 about it. I mean, I want to -- I want to -- I

C E R T I F I C A T E

STATE OF DELAWARE)
) ss:
COUNTY OF NEW CASTLE)

I, Deanna L. Warner, a Certified Shorthand Reporter, do hereby certify that as such Certified Shorthand Reporter, I was present at and reported in Stenotype shorthand the above and foregoing proceedings in Case Number 19-2100-MSG, *AZURITY PHARMACEUTICALS, INC. vs. ALKEM LABORATORIES, LTD.*, heard on August 18, 2022.

I further certify that a transcript of my shorthand notes was typed and that the foregoing transcript, consisting of 98 typewritten pages, is a true copy of said **BENCH TRIAL.**

SIGNED, OFFICIALLY SEALED, and FILED
with the Clerk of the District Court, NEW
CASTLE County, Delaware, this 26th day of
August, 2022.

Deanna L. Warner, CSR, #1687
Speedbudget Enterprises, LLC

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC.,)	
)	
Plaintiff,)	
)	
v.)	C.A. No. 19-2100 (MSG)
)	
ALKEM LABORATORIES LTD.,)	CONFIDENTIAL –
)	FILED UNDER SEAL
Defendant.)	

**PLAINTIFF AZURITY PHARMACEUTICALS, INC.’S
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September 15, 2022

I. INTRODUCTION

Azurity's mission is to bring high-quality medicines to underserved and overlooked patient populations, namely children and the elderly. In 2016, after enalapril had been available in tablet form for over 30 years, Azurity developed ready-to-use liquid oral formulations of enalapril. These liquid formulations of enalapril were designed to be stable for at least 12 months, and safe and reliable for these overlooked patient populations—medicine that greatly improved upon the enalapril options previously available for patients that could not take pills. The Asserted Claims cover these novel formulations of enalapril. Seeking to replicate Azurity's success, Alkem submitted an ANDA to FDA for a generic version of Azurity's proprietary Epaned[®] product, which directly copied a formulation from Azurity's Asserted Patents.

At trial, Azurity demonstrated by a preponderance of the evidence that Alkem literally infringes the Asserted Claims. Alkem's single noninfringement defense to the '621 patent, the optional addition of sodium hydroxide or hydrochloric acid, lacks merit and does not circumvent infringement.

Alkem also failed to prove by clear and convincing evidence that the Asserted Claims are invalid for obviousness, lack of written description, or indefiniteness. As to obviousness, Alkem's analysis is plagued with improper hindsight and relies on prior art references that have massive holes. Most notably, Alkem failed to identify any prior art reference disclosing a liquid enalapril formulation that was stable for at least 12 months or any reference teaching that such a formulation was even feasible. To fill that fatal hole in the prior art, Alkem argues in conclusory fashion that long term stability was a matter of "routine optimization" or "routine experimentation." But the (1) absence of any prior art liquid enalapril formulation that was stable for more than 3 months and (2) the known instability of enalapril in water, show that the challenge facing a POSA was far more than "routine." In addition, the objective indicia of nonobviousness are strong: the claimed invention of the Asserted Patents provided unexpected stability, succeeded where all others had failed, and filled a long-felt but unsolved need at the time of the invention.

Alkem failed to prove by clear and convincing evidence that the Asserted Claims are invalid for lack of written description. The four corners of the specification describe every aspect of the Asserted Claims such that a POSA would understand that Azurity invented them. Alkem's insistence otherwise arises from an incorrect understanding of the law. For example, Alkem's expert testified that the specification must provide at least 12 months of stability data for the formulations described in the Asserted Claims. However, the law does not require actual reduction to practice or actual examples of the invention. Thus, application of the correct legal standard shows that Alkem fell well short of meeting its burden of clear and convincing evidence.

Lastly, Alkem failed to prove by clear and convincing evidence that the Asserted Claims of the '621 patent are indefinite due to the presence of the term "stable" in each claim. Alkem's purported evidence is contradicted by the express and unambiguous language in each Asserted Claim of the '621 patent that explains the stability requirement, which mirrors the unambiguous definition of the term "stable" that appears in the specification. Based on the content of the claims and specification, a POSA would have a firm understanding of the stability requirement in each claim. Alkem fell well short of meeting its clear and convincing burden of proof regarding indefiniteness.¹

Azurity respectfully requests the Court to enter judgment in its favor and grant all available and pertinent relief, including an injunction under 35 U.S.C. § 271(e)(4)(B) precluding Alkem from launching its ANDA Product until expiration of the Asserted Patents.

¹ Since trial, Alkem has withdrawn three defenses: (1) its only noninfringement defense to the '482 patent, withdrawn on August 24, 2022 (D.I. 189; *see also* Tr. 204:14-206:16); (2) its inventorship defense (*see* Tr. 340:21-23, 449:1-450:1), withdrawn on September 12, 2022; and (3) its enablement defense (*see* Tr. 339:6-19), withdrawn on September 14, 2022. Based on Alkem's representations, Azurity will not address these arguments in post-trial briefing.

disclose buffer concentration range), 366:18-21 (Epaned Kit Insert does not disclose buffer concentration range), 369:7-10 (Sosnowska does not use sodium citrate, the buffer in the claims, in formulations). Thus, there is no evidence how or why a POSA would arrive at the claimed buffer concentrations when attempting to modify the prior art to achieve a liquid enalapril formulation that is stable for at least 12 months.

Dr. Constantinides attempted to characterize the claimed buffer concentrations as general knowledge or “basic colloquia” that a POSA would just know or be able to calculate. Tr. 291:15-22. Despite this “minor” “high school and college” skill regarding “how you calculate buffer concentrations” (Tr. 290:16-291:1), Dr. Constantinides never attempted to perform calculations (Tr. 354:20-355:2), nor did he provide any evidence that the calculations described in de Villiers would necessarily lead to the claimed buffer concentrations. Tr. 352:11-15, 353:1-8. Thus, there is no evidence that the claimed buffer concentrations were disclosed in the prior art, nor any evidence that a POSA would necessarily arrive at the claimed buffer concentrations by using any of the calculations in de Villiers. That absence of evidence is fatal to Alkem’s theory that the Asserted Claims are obvious. *Santarus, Inc. v. Parm Pharm., Inc.*, 694 F.3d 1344, 1357 (Fed. Cir. 2012) (reversing district court judgement of obviousness because the claims required a specific amount of buffering agent that was not disclosed in the prior art).

c. Alkem Provided Insufficient Evidence Regarding the pH Limitation “About 3.3” (’482 Patent, Claim 22; ’621 Patent, Claim 7) and “Less Than 4.5” (All Other Asserted Claims)

Alkem asserts that a POSA looking to create a stable solution would choose a formulation with a pH of 3 because, as Alkem claims, the “maximum stability, chemical stability for the drug is around pH 3.” Tr. 257:1-3. However, Dr. Constantinides admitted that the Allen reference cites to the Merck index for the proposition that enalapril is maximally stable at a pH of about 3 (Tr. 348:17-349:15), and the Merck index says nothing about the pH at which enalapril is maximally

Additionally, Dr. Constantinides' reliance on de Villiers is misplaced. de Villiers does not disclose any pH values related to enalapril formulations or provide any evidence or support that a pH of about 4.5 or below is disclosed in any of the cited references. Tr. 375:7-12; *see generally*, DTX-1118.

Finally, other prior art relied on by Dr. Constantinides illustrates that he cherry-picked his evidence regarding the pH limitations. For example, the pH of the liquid enalapril formulations discussed in the Nahata reference actually teaches away from a pH of about 4.5 or below. *E.g.*, DTX-1078 at 1156, Table 1 (disclosing liquid enalapril formulations having, *e.g.*, pH 7.1 and 5.1); Tr. 514:12-23 (discussing same).

d. Alkem Provided Insufficient Evidence Regarding the Sucralose Limitation ('482 Patent, Claim 16)

Alkem failed to provide clear and convincing evidence that a POSA would select sucralose as a sweetener in a liquid enalapril formulation that is stable for at least 12 months. Testimony from Alkem's own expert establishes that a POSA who used a prior art enalapril formulation as a starting point would not substitute sucralose for the sweeteners used in prior art formulations. On cross-examination, Dr. Constantinides testified that a POSA using the prior art Kit Insert as a starting point for a 12-month stable liquid enalapril formulation would keep the two sweeteners already used in the Kit product. Tr. 304:11-305:1; DTX-1073 at § 11. He testified specifically that a POSA would **not** substitute sucralose for the sweeteners listed in the Kit Insert. Tr. 367:25-368:16.

Therefore, Alkem failed to show by clear and convincing evidence that claim 16 of the '482 patent would have been obvious to a POSA. A POSA lacked any reason or motivation to use sucralose as required in claim 16.

e. Alkem Provided Insufficient Evidence Regarding the “No Mannitol” Limitation (’482 Patent, Claim 18)

Alkem failed to provide clear and convincing evidence that a POSA would exclude mannitol from a liquid enalapril formulation that is stable for at least 12 months. Mannitol is found in prior art enalapril formulations, including the ’747 patent (which used mannitol as a “stability agent” DTX-1094 at 5:49-50, Examples 1-4) and the Kit Insert (which did not describe the function of mannitol DTX-1073 at § 11). The formulations of the ’747 Patent that included mannitol were the most stable. Tr. 491:10-22; DTX-1094 at 23:39-40. A POSA using the prior art as a starting point would have no reason to remove mannitol to create a liquid enalapril formulation that is stable for at least 12 months. Tr. 491:5-493:13, 531:13-21. Among other reasons, mannitol’s function as a stabilizer would cause a POSA to retain mannitol in the formulation, not remove it. Tr. 491:23-492:22, 531:13-21.

The only evidence to the contrary provided by Alkem is the unsupported testimony of Dr. Constantinides, who described mannitol as a “bulking agent” and said that it is used “primarily for solid dosage forms.” Tr. 264:24-265:14. However, mannitol is also used in liquid formulations, including examples that appear in the specification of the Asserted Patents. Tr. 492:22-493:3; PTX-1 at 33:52 (Table C-1). Dr. Little testified that he has found mannitol to be useful in liquid formulations. Tr. 493:10-13. Thus, a POSA would have no reason to remove the mannitol when creating a ready-to-use formulation, especially when the prior art ’747 Patent shows that mannitol enhances stability and states that mannitol was added as “something to stabilize the formulation,” DTX-1094 at 5:49-50, Tr. 491:9-22. Dr. Constantinides’ unsupported testimony alone is neither clear nor convincing evidence that a POSA would have removed mannitol when attempting to develop a liquid enalapril formulation that is stable for at least 12 months.

Therefore, Alkem failed to show by clear and convincing evidence that claim 18 of the '482 Patent would have been obvious to a POSA.

2. Alkem Failed to Show a Motivation to Combine the Prior Art

Alkem also failed to show clear and convincing evidence of a motivation to combine any of its prior art references. The only alleged motivation Alkem identified is a statement in a 1998 publication by Nahata that a commercially available, liquid formulation of enalapril does not exist. Tr. 266:21-267:10 (“[T]here is no liquid dosage for—it’s commercially available for pediatric patients . . . [s]o that would motivate the POSA than indeed an oral liquid formulation, a ready-to-use liquid formulation, it’s a medical need . . .”). However, the identification of a need alone is insufficient. There must be motivation to combine specific attributes taught in the prior art to achieve a specific result:

[M]ere identification in the prior art of each component of a composition does not show that the combination as a whole lacks the necessary attributes for patentability, *i.e.* is obvious. . . . Rather, to establish a *prima facie* case of obviousness based on a combination of elements in the prior art, the law requires ***a motivation to select the references and to combine them in the particular claimed manner*** to reach the claimed invention.

Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369, 1379-80 (Fed. Cir. 2006)); Tr. 512:24-513:8 (“[Y]ou can have a motivation to make it in the first place, so that could be that it’s safer. But there also needs to be a specific reason why somebody would have combined the specific references that have been put forth in order to achieve the specific invention that we’re talking about.”). Further, “[t]he showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence.” *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1334 (Fed. Cir. 2002) (finding expert’s “conclusory assertion” that nature of the problem provided sufficient motivation to combine two references was insufficient and based on hindsight).

the Asserted Claims '621 patent is unambiguous. Tr. 458:12-22. Dr. Constantinides provided no testimony to the contrary.

Alkem thus failed to provide clear and convincing evidence of indefiniteness arising from the term “stable” used in the Asserted Claims of the '621 patent.

V. CONCLUSION

Azurity met its burden of proving infringement by a preponderance of the evidence. Alkem failed to provide clear and convincing evidence supporting any of its invalidity defenses. Azurity respectfully requests that judgment be entered in favor of Azurity.

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September 15, 2022

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC.

Plaintiff,

v.

ALKEM LABORATORIES LTD.,

Defendant.

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C.A. No. 1:19-CV-02100-MSG

**CONFIDENTIAL – FILED
UNDER SEAL**

DEFENDANT, ALKEM LABORATORIES LIMITED'S POST-TRIAL BRIEF

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Dated: September 15, 2022

TABLE OF CONTENTS

I.	OVERVIEW	2
II.	NONINFRINGEMENT	7
A.	Alkem’s ANDA Product Will Include NaOH.	7
B.	Plaintiff Failed to Prove Alkem’s Product Meets the Asserted Buffer Limitations	11
C.	Alkem’s Addition of NaOH Precludes Infringement as to the ’621 Patent.....	12
III.	INVALIDITY	15
A.	Alkem Proved by Clear and Convincing Evidence that the Patents-in-Suit Fail to Satisfy the Written Description for the Formulations Claimed as Being Preserved with a Single Paraben.	15
B.	Alkem Proved by Clear and Convincing Evidence that the Patents-in-Suit Fail to Satisfy the Written Description for the Formulations Claimed as Being Preserved with a Mixture of Parabens That Meet the 12-Month or Longer Stability Claim Element	18
C.	Obviousness	19
i.	Prior Art Formulations Read Directly on the Asserted Claims	21
ii.	By Dr. Little’s Own Elegant Standard, Modifying the Prior Art Formulations to Stabilize Them Would Require No Undue Experimentation.....	26
iii.	Additional Inconsistency in Dr. Little’s Testimony	28
iv.	Motivation to Combine the Prior Art Teachings	28
v.	Dr. Little Identified No Teaching Away from the Claimed Inventions.....	30
vi.	Plaintiff Failed to Adduce Relevant Evidence of Secondary Considerations of Nonobviousness.....	31
1.	Plaintiff Failed to Adduce Evidence of a Nexus Between Any Secondary Consideration of Nonobviousness and the Asserted Claims.	31
2.	Plaintiff Failed to Demonstrate the Asserted Claims Satisfied A Long Felt-Need	33
a.	Nexus aside, Plaintiff’s Theory is Untethered to the Asserted Claims	33
b.	Plaintiff Failed to Demonstrate Any Need the Asserted Claims Satisfied	36
3.	Plaintiff Failed to Adduce Evidence of Unexpected Results.....	37

4.	Plaintiff Failed to Adduce Any Evidence of Other Secondary Considerations.....	38
5.	The U.S. Patent and Trademark Office’s (“USPTO”) Finding of Obviousness Should Be Given Deference.	38
6.	Obviousness Conclusion.....	39
IV.	CONCLUSION.....	40

In this case, according to Dr. Little, the claimed formulations are novel due to their stability, but the stability of the claimed formulations from the '621 patent are not in any way linked to NaOH, which is not listed as an ingredient. And, as Dr. Little admitted, Plaintiff cannot prove Alkem's product meets the claimed stability limitations without the addition of NaOH. Therefore, Plaintiff cannot prove infringement of the '621 patent claims, and Alkem respectfully requests entry of judgment of noninfringement on all such claims.

III. INVALIDITY

Alkem maintains the Asserted Claims are invalid for at least four reasons, the first two of which are related: Dr. Little's self-serving, conclusory testimony notwithstanding, Alkem demonstrated by clear and convincing evidence that the '482 and '621 patents lack sufficient information regarding formulations preserved with parabens to provide a basis to POSAs to conclude that the inventors had possession of either (1) single-paraben preserved formulations (as claimed in the Asserted Claims; or (2) multiple paraben-preserved formulations with the claimed stability. Furthermore, Alkem demonstrated by clear and convincing evidence that the claimed formulations, which are identical to prior art formulations, would be obvious to POSAs as of the priority date of the alleged inventions.

A. **Alkem Proved by Clear and Convincing Evidence that the Patents-in-Suit Fail to Satisfy the Written Description for the Formulations Claimed as Being Preserved with a Single Paraben.**

Each of the Asserted Claims is directed to formulations that include "a preservative, wherein the preservative is a paraben or mixture of parabens." (*See* Asserted Claims (emphasis added).) Yet, the patents-in-suit provide no information whatsoever regarding any formulations comprising as "the preservative . . . a paraben." (*See generally* PTX-1, PTX-2; *see also* Trial Tr. 330:12-335:6.) Moreover, the inventors never even tried to preserve an enalapril formulation—or

any other kind formulation—using only a single paraben, because they didn’t think it would work. (See Mosher Dep. Tr. at 86:22-88:11; 91:10-15 (discussed *infra*).)

Each paraben-containing example in the patents-in-suit is preserved with either a combination of parabens (with or without a third preservative) or a paraben combined with another preservative, such as potassium sorbate or sodium benzoate. (See, e.g., PTX-1 at Col. 31, Table A-1, Examples A5 and A6 (preserved with paraben and sodium benzoate and paraben and potassium sorbate, respectively); *id.* at Table C-1, Examples C1-C5 (preserved with multiple parabens in addition to either sodium benzoate or potassium sorbate (C1-C3) or a single paraben combined with either sodium benzoate or potassium sorbate (C4, C5); *see also* Trial Tr. 25:19-22 (Plaintiff counsel acknowledging sodium benzoate as a preservative); Trial Tr. 287:15-23 (describing potassium sorbate as a preservative).) Moreover all of the data submitted by the patent applicants to the U.S. Patent and Trademark Office (“USPTO”)—by way of affidavits by named inventor Dr. Mosher—described formulations preserved exclusively with sodium benzoate. (See Trial Tr. 324:17-325:24 (Dr. Constantinides testifying); *id.* at 468:12-19 (Dr. Little agreeing with Dr. Constantinides’s testimony on the relevant point.))

To attempt to overcome these deficiencies, Plaintiff points to one or more prior art formulations using parabens as preservatives, including one described as “methyl hydro benzoate,” which Dr. Little testified was methylparaben (*see* Trial Tr. 516:7-25), and information within the patents-in-suit that Dr. Little contends—without explanation—somehow guides POSAs to making single-paraben formulations. But, a blanket, conclusory reference to prior art examples using a single paraben preservative, particularly without further explanation as to how a POSA would use that single paraben to work as claimed in the claimed formulations, is of no use to the Court. *See, e.g., Ariad Pharm., Inc., v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (noting

that written description is based on the information within the “four corners” of the specification as of the patent filing date); *see also Biogen Int’l GmbH v. Mylan Pharms, Inc.*, 18 F.4th 1333, 1341-42 (Fed. Cir. 2021) (same). More significantly, however, in pointing to information within the patents regarding paraben-preserved formulations, to the extent Dr. Little is referring to formulations preserved with only a single paraben, he is pointing to information that the lead inventor, and preservative selector Dr. Mosher testified at deposition does not exist.

Both Plaintiff and Dr. Little ignored clear, unequivocal and conclusive evidence that the patents are deficient with respect to formulations preserved with a single paraben: At his deposition, the lead inventor Dr. Mosher, who was responsible for ingredient selection generally and preservative selection specifically (*see* Mosher Dep. Tr. at 75:7-12 (admitting he was responsible for preservative selection)), admitted that the inventors never even attempted to formulate a product preserved with only a single paraben because it was Dr. Mosher’s “understanding from the literature that a single paraben does not have the breadth of antimicrobial activity as the combination.” (*See id.* at 86:22-88:11 (testifying that he would not know how a single paraben would perform in formulation); *id.* at 91:10-15 (Dr. Mosher admitting he has never formulated a drug product using a single paraben).)

To the extent Dr. Little is pointing to the patents-in-suit as evidence of information the inventor testified he did not have in his possession, Dr. Little’s conclusion clearly is baseless. Regardless, Plaintiff offered only Dr. Little’s conclusory assertions to attempt to rebut Alkem’s written description and non-enablement arguments, and Alkem respectfully submits those are insufficient to overcome the inventor’s deposition admissions as clear and convincing evidence of lack of written description. (*See id.*; *see also id.* at 85:21-88:11.) *See, e.g., ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1379 (Fed. Cir. 2009) (a specification satisfies the written

description requirement only “if the description . . . clearly allow[s] persons of ordinary skill in the art to recognize that the inventor invented what is claimed” and “had possession of the claimed subject matter as of the filing date”).

The patents-in-suit could not possibly provide a basis for a POSA to conclude that the inventors possessed that which the lead inventor admitted he did not try because he could not do. *See Wyeth v. Abbott Labs.*, C.A. No. 08-230, 2012 U.S. Dist. LEXIS 6869, at *24 (D. Del. Jan. 19, 2012) (“Logically, the inventors could not have described a knowledge they did not possess.” (internal quotations, corrections omitted) (quoting *Boston Sci. Corp. v. Johnson & Johnson*, 679 F. Supp. 2d 539, 555 (D. Del. 2010)). The facts of the *Wyeth* case are illustrative. There, the Court rejected a patent defender’s post-patent efforts to fill in the gap of the inventors’ knowledge. *See id.* at *24-*25. Respectfully, the Court should do the same.

Alkem has proven by clear and convincing evidence that that the ’482 and ’621 patents fail to meet the written description requirements with respect to formulations preserved with only a single paraben, as claimed in the Asserted Claims. Therefore, the Asserted Claims are invalid under 35 U.S.C. § 112.

B. Alkem Proved by Clear and Convincing Evidence that the Patents-in-Suit Fail to Satisfy the Written Description for the Formulations Claimed as Being Preserved with a Mixture of Parabens That Meet the 12-Month or Longer Stability Claim Element

The same rationale supports finding that the inventors failed to adequately describe and/or enable formulations preserved with a mixture of parabens as well, though the analysis is complicated by the fact that the patents-in-suit describe such formulations (unlike the theoretical formulations comprising a single paraben as a preservative) and include short-term stability data pertaining to the same. Alkem nonetheless respectfully submits that, to the extent Plaintiff purports to establish written description of mixed paraben formulations by reference to the 180-

day and eight-week stability results depicted in the patents-in-suit, they should be foreclosed from doing so by Dr. Little's contrary testimony that POSAs would not trust such data because "these reactions, as I testified, they can fall off a cliff." (*See* Trial Tr. 548:6-549:5.)

To be clear, Alkem contends, consistent with its own expert's testimony, as well as Dr. Little's (in places) and Dr. Mosher's, that POSAs know how to and routinely extrapolate and rely upon long-term stability data estimates based on short-term data using accelerated studies in doing their day-to-day drug development work. (*See* Trial Tr. 294:5-295:17 (Dr. Constantinides discussing influence of FDA guidance and describing accelerated studies); Trial Tr. 549:6-549:14 (Dr. Little reluctantly agreeing that formulators use accelerated studies to extrapolate long-term stability data from short-term stability data); *see also generally* Mosher Dep. Tr. 25:21-32:4; 58:11-59:6; 87:14-89:19 (describing a formulator's approach to formulation).) What such a study might say about the paraben formulations from the A or C examples in the patents-in-suit is anyone's guess, however. Dr. Little never testified to that fact, another reason the Court is free to discount his conclusions.

C. Obviousness

Plaintiff is seeking to protect its second-generation enalapril product with patents that, while they do not cover a currently commercialized product, claim formulations that are practically identical to formulations described in the prior art Alkem presented at trial. Moreover, both Alkem's and Plaintiff's expert witnesses described the abilities of POSAs such that they easily would have known how to tweak the prior art formulations to extend Plaintiff's own patent-protected first-generation product's shelf life.

Plaintiff's own expert Dr. Mahan testified at length as to at least one motivation that existed prior to the patents to do so, though the motivation likewise springs from the prior art itself,

(as compared to related patent claims, including those that Plaintiff's Epaned product actually practices) is the preservative component, which is "a paraben or a mixture of parabens," but the record is devoid of evidence that the paraben preservatives confer any sort of benefit at all other than their expected antimicrobial action, which is not unique to paraben combinations. (*See* Trial Tr. 85:4-86:21 (Dr. Mosher explaining why he chose sodium benzoate over parabens as the preservative for the second-generation Epaned product).)

Indeed, even if Alkem were to accept Plaintiff's assertion that Alkem's product practices the claimed invention (it does not due to (a) Plaintiff's failure to prove the buffer limitation and (b) the addition of NaOH)), its expert Dr. Mahan eliminated all possibility of establishing nexus when he described Alkem's product as, from a clinical perspective, "basically the same thing" as Plaintiff's Epaned product. (*See* Trial 426:1-3.)

Alkem's prior art reads directly on the asserted claims, and the record at trial is clear that POSAS, as defined by Plaintiff's own expert, would have the knowledge and motivation to tweak those formulation to provide for a stable oral liquid formulation of enalapril for two years or greater with a reasonable expectation of arriving at the claimed inventions without undue experimentation. Plaintiff failed to overcome this strong case of obviousness.

i. Prior Art Formulations Read Directly on the Asserted Claims

Alkem must prove by clear and convincing evidence that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *Pfizer v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007) (stating the relevant standard). The obviousness analysis requires the Court to compare the Asserted Claims with the prior art as of the earliest possible effective filing date, which in this case the parties agree is March 18, 2016. *See* 35 U.S.C. § 103 (2022); *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)

could be described as a relic from the stone age of medicine (*see* Trial Tr. 66:18-22; 68:21-69:19; 104:5-21). Whereas DNA may be digital, the record demonstrates enalapril is analog.

Plaintiff's response to this comparison, no doubt, will be to attack the stability data regarding these formulations as somehow unreliable,¹² despite the fact the inventors of the patents-in-suit rely on even shorter-term stability data, with which Dr. Little takes no issue.

ii. By Dr. Little's Own Elegant Standard, Modifying the Prior Art Formulations to Stabilize Them Would Require No Undue Experimentation

To be sure, Dr. Constantinides offered ample, consistent testimony clearly establishing the routineness of the stability testing that would be required to tweak the prior art formulations to reach the claimed inventions. (*See, e.g.*, Trial Tr. 300:4-23, 313:18-23 (discussing routineness of determining and testing buffer concentrations), 315:2-316:14 (routineness of stability testing) ; *cf.* Mosher Dep. Tr. 59:16-61:10 (describing buffer interchangeability), 87:14-89:19 (refusing to use the word "routine" but agreeing antimicrobial testing on parabens would be "standard" or "commonly used").) But, no witness at trial articulated so clearly such a simple and elegant assessment of a POSA's capabilities as Plaintiff's expert Dr. Little. Throughout this brief, Alkem has pointed to inconsistencies in Dr. Little's testimony that amply demonstrate his bias, lack of independence and unreliability. No example yet discussed, however, is quite so detrimental to Plaintiff's obviousness rebuttal as when Dr. Little endorsed a standard for finding obviousness, although he did so in the context of trying to rebut Alkem's written description arguments. Pointing (i) generally to otherwise undescribed prior art formulations containing parabens and (ii) the totally conclusory disclosures in the patents-in-suit, including disclosures the inventor Dr. Mosher admitted could not possibly have been in the patents-in-suit as well as, presumably, the

¹² It seems less likely Plaintiff will point out the inconsistency between this position and the positions Dr. Little asserted at trial in defense of the patents-in-suit. (*See supra*, throughout.)

short-term stability data from the patents-in-suit that Dr. Little dismisses when evaluating the prior art for obviousness, Dr. Little pieced the breadcrumbs together precisely the way Dr. Constantinides testified a POSA would do and said this, specifically about parabens: “They’re able to be tested for stability, so there’s no reason to believe that somebody would have undue experimentation in in making these embodiments which are described in the specification and testing them for stability.” (*see* Trial Tr. 468:20-469:22.)¹³

Dr. Little is incorrect about the teachings of the patents-in-suit, in particular regarding single-paraben formulations. Dr. Mosher made that clear at his deposition. He is correct, however, about the ease with which POSAs would have approached stabilizing drug product ingredients already known to be stable: “They’re able to be tested for stability, so there no reason to believe that someone would have undue experimentation” stabilizing them. *See id.*

If the prior art Alkem presented at trial and discussed above demonstrates nothing else, it demonstrates that enalapril was able to be tested for stability and in fact had proven stable in various formulations for up to 12 weeks with reasons to hope for longer. Thus, to paraphrase Dr. Little, because enalapril could be tested for stability, “there’s no reason to believe that someone would have undue experimentation” stabilizing it in the prior art formulations.

Dr. Little should not be permitted to hold the prior art and short-term stability data to two different standards depending upon which argument he is trying to defend. His elegant and

¹³ Dr. Little’s conclusion is squarely at odds with inventor Dr. Mosher’s testimony that he never tried to formulate using a single paraben preservative because he did not think it would work. Dr. Little also points to prior art cautions about preservatives, generally, and parabens, specifically—none of which would be considered teaching away as a legal matter—in addressing obviousness, but Dr. Little ignores those cautions altogether—including cautions in the patents-in-suits themselves—when discussing parabens in the context of the patents. (*See* Trial Tr. 518:8 to 519:16; *see also* PTX-1 at 13:8-15 (cautioning about mixing parabens with certain sugars and sugar alcohols in enalapril formulations).)

practical standard for defending the patents—mistakenly premised as it was on a disingenuous acceptance of prior art and short-term stability data not to mention his grossly mistaken belief about the quality of the information in the patent regarding paraben formulations—as verified by inventor Dr. Mosher—is the one that should guide the Court in deciding what POSAs would do under the circumstances before the Court: If POSAs can test it for stability, there is no reason to believe undue experimentation would be needed to stabilize the prior art enalapril formulations.

iii. Additional Inconsistency in Dr. Little’s Testimony

Dr. Little seems embrace two alternate and totally incompatible versions of a POSA; one looking at prior art for obviousness who is an incredibly fearful POSA deterred where others would be inspired, the other, looking at prior art for the purpose of bolstering the patents-in-suit, a bold POSA naturally curious and inclined to apply their knowledge and skills to advance science. Plaintiff should not benefit from Dr. Little’s unabashed inconsistencies. Dr. Little applies one standard for obviousness and an entirely different standard when defending the sufficiency of the patents. (*Contrast, e.g.*, Trial Tr. 548:20-549:5 (Dr. Little describing short-term stability data as unreliable because “they can fall off a cliff”) *with* Trial Tr. 466:11-469:22 (Dr. Little describing the patents as enabling and erroneously describing the short-term stability data for paraben formulations in the patents-in-suit as “long-term stable formulations”); *see also* Trial Tr. 551:20-552:8 (dismissing prior art short-term stability data because it did not “guarantee” long-term results).) His testimony regarding all of the prior art should be discounted accordingly.

iv. Motivation to Combine the Prior Art Teachings

Alkem offered clear, consistent expert testimony regarding the specific motivations that would lead a POSA to combine the prior art teachings (*see* Trial Tr. 265:21-267:10 (motivation and the Nahata reference, DTX-1078), 299:7-18 (motivation to move from reconstituted formulations to long-term stable liquid formulations); 303:3-8 (motivation to use water); 303:9-

304:6 (motivation from FDA guidance); 307:4-9 (motivation to formulate to a pH of ~3.3); 307:10-308:14 (motivation to pursue long-term stability); 308:15-309:8 (motivation to use and optimize buffers); 312:22-313:23 (motivation to formulate at or below pH 4.5 and optimize buffers); 315:2-316:14 (motivation to formulate liquid formulations of enalapril with long-term stability and other features).¹⁴ Yet, the evidence is likewise clear that modifying the prior art formulations to arrive at the claimed inventions was well within the knowledge and skills of a POSA and, thus, literally combining the prior art is not necessary. Indeed, Dr. Little's own standard for defending the patents-in-suit on written description and enablement clearly establish that a POSA would have no trouble modifying the prior art formulations without undue experimentations because both enalapril and the prior art liquid enalapril formulations all demonstrated stability to a significant degree. (*See* Trial Tr. 468:20-469:22 (Dr. Little referring to parabens in prior art formulations: "They're able to be tested for stability, so there's no reason to believe that somebody would have undue experimentation in in making these embodiments which are described in the specification and testing them for stability.").)

To paraphrase Bob Dylan, the Court does not need an expert to know which way the wind is blowing. Motivation to combine the prior art springs from the pages of Alkem's prior art references themselves, and, in any case, Dr. Constantinides' testimony regarding motivation establishes clearly and convincingly that a POSA would be motivated by the teachings in the references discussing enalapril formulations to modify those formulations to improve the long-

¹⁴ Plaintiff undoubtedly will argue that Dr. Constantinides engaged in hindsight reasoning. The record, which is brimming with testimony on motivation that is not at all in the nature of hindsight reasoning, does not support that conclusion, and Alkem respectfully submits that Dr. Constantinides's off-hand remark at the end of a long deposition day does not remotely off-set his testimony or raise a legitimate question as to hindsight.

term stability of those formulations with at least a reasonable expectation of successfully arriving at the Asserted Claims.

v. Dr. Little Identified No Teaching Away from the Claimed Inventions.

When Dr. Little looks at the prior art for obviousness, he sees only roadblocks and warning signs. As detailed *supra*, he looks at it differently when he needs it to supplement the patents-in-suit. In any case, nowhere in the prior art did Dr. Little point to a single instance wherein someone tried and failed to create an enalapril formulation with the long-term stability claimed in the patents-in-suit. (*See* Trial Tr. 557:22-559:9 (Dr. Little reluctantly agreeing that Alkem’s prior art did not fail to meet a stated objective).) Moreover, Dr. Little pointed to nothing in the prior art discussing enalapril formulations that would constitute a teaching away in the obviousness analysis. *See Trs. of Columbia Univ. in N.Y. v. Illumina, Inc.*, 842 Fed. App’x 619, 624-25 (Fed. Cir. 2021) (“Teaching away requires clear discouragement from implementing a technical feature,” and “just because better alternatives exist in the prior art does not mean that an inferior alternative is inapt for obviousness purposes” (internal quotations omitted)). Instead, Dr. Little pointed to the passage of time as somehow being an indication of obviousness, but he does not seem to have considered the protective, or blocking, effects of Silvergate’s and Merck’s intellectual property covering enalapril (*see* Trial Tr. 86:9-17 (Mr. Beckloff testifying that Merck invented enalapril), 88:1-10 (Mr. Beckloff acknowledging being an inventor on the ’747 patent prior art reference, DTX-1094); *see also* FDA Orange Book entry for the Epaned Kit at https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=204308&Appl_type=N (identifying the ’747 patent as currently listed for the product) (last checked September 15, 2022), and he also seems unaware of the Federal Circuit’s holding, “Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed

Dated: September 15, 2022

Respectfully submitted,

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC.,)	
)	
Plaintiff,)	
)	
v.)	C.A. No. 19-2100 (MSG)
)	
ALKEM LABORATORIES LTD.,)	CONFIDENTIAL –
)	FILED UNDER SEAL
Defendant.)	

**PLAINTIFF AZURITY PHARMACEUTICALS, INC.’S
SUPPLEMENTAL POST-TRIAL BRIEF**

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October 14, 2022

IV. QUESTION 4

To prove that claim 16 of the '482 patent would have been obvious, Alkem was required to prove, by clear and convincing evidence that it would have been obvious to a POSA to modify the prior art to create an oral liquid formulation with all of the limitations of claim 16,⁷ including, specifically, a sweetener that is sucralose. *Procter & Gamble*, 566 F.3d at 994. To meet this burden, Alkem must have shown that the POSA “would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *Id.*; *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1372 (Fed. Cir. 2017). The claim limitation “wherein the sweetener is sucralose” cannot be divorced from all of the other limitations of claim 16—the claim must be analyzed “as a whole.” 35 U.S.C. § 103; *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1379-80 (Fed. Cir. 2006) (“[M]ere identification in the prior art of each component of a composition does not show that the combination *as a whole* lacks the necessary attributes for patentability, i.e. is obvious.”).

A. The Evidence At Trial Demonstrated That A POSA Would Not Have Been Motivated To Create The Formulation Of Claim 16, Including Sucralose

The evidence presented at trial shows that prior to the invention of the Asserted Patents, a POSA would not have preferred sucralose over other sweeteners. The prior art Kit formulation did not contain sucralose, nor did the formulations in the Allen reference. DTX-1073 at § 11; DTX-1074 at 1919, nn. f-h. In fact, Alkem’s expert admitted that a POSA using the prior art Kit Insert as a starting point would *not* be motivated to change the sweeteners that were included in that formulation:

⁷ Claim 16 depends from claims 14 and 15, and therefore includes all of the limitations recited in those claims.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

— — —

AZURITY PHARMACEUTICALS, : CIVIL NO. 19-2100
INC., :
Plaintiff :

V.

ALKEM LABORATORIES, : Philadelphia, Pennsylvania
LTD., : January 19, 2023
Defendant : 10:00 a.m.

— — —

TRANSCRIPT OF ORAL ARGUMENT
BEFORE THE HONORABLE MITCHELL S. GOLDBERG
UNITED STATES DISTRICT COURT JUDGE

— — —

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1 THE COURT: The doc -- before you do that,
2 the last testimony that you referenced for Dr.
3 Little --

4 MR. KRATZ: Yes.

5 THE COURT: -- at some point -- you don't
6 have to do it now because it will interrupt your
7 flow, but at some point could you and/or your team
8 give us some page numbers for that?

9 MR. KRATZ: It's -- we have a slide for it.
10 It's slide 81.

11 THE COURT: Slide 81?

12 MR. KRATZ: Yes.

13 THE COURT: Thank you. Okay, go ahead.

14 MR. KRATZ: So written description is a
15 requirement under Section 112 of the Patent Act. As
16 an overview -- and let me start by saying that most
17 of the trial was a discussion about obviousness, and
18 there was some about infringement. The trial doesn't
19 have a lot in the argument -- or in the evidence that
20 was being brought in about written description. It's
21 a legal requirement.

22 THE COURT: Yes.

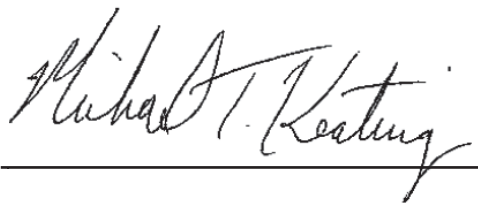
23 MR. KRATZ: And that's why. So I want
24 to -- the importance of written description, we went
25 last with it in this -- in this closing argument.

CERTIFICATION

I, Michael Keating, do hereby certify that
the foregoing is a true and correct transcript from the
electronic sound recordings of the proceedings in the
above-captioned matter.

1/27/23

Date

A handwritten signature in cursive script, reading "Michael T. Keating", written over a horizontal line.

Michael Keating

Exhibit A

CURRICULUM VITAE OF PANAYIOTIS P. CONSTANTINIDES

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EXECUTIVE SUMMARY

Career Objectives: *Expand therapeutic utility and market value of small molecule and macromolecule drugs, approved and New Molecular Entities (NMEs), from innovative drug formulation and delivery technology, product development and commercialization, life-cycle management, strategic partnerships and business development perspectives.*

Education: University Diploma/B.Sc. *Chemistry*, 1977 (Athens University), Ph.D., *Biochemistry*, 1983 (Brown University), Postdoctoral Training, *Pharmacology/Cancer Research*, 1983-1985 (Yale University).

Industrial Experience: Big Pharma (8 yrs), Specialty Pharma/Drug Delivery/Biotech (9 yrs); consultant (16 yrs). **Dosage Forms:** parenteral (intravenous solutions, liposomes, micelles, emulsions, micro-/nanoparticles, cyclodextrins; liquid and lyophilized formulations); oral hard and soft gelatin capsules (liquid, suspension, semi-solid fill); immediate and controlled release tablets and capsules; nasal sprays and topical formulations (foams, gels, creams, ointments). **Drug Molecules:** Small molecule and macromolecules (peptides, proteins and vaccines); BCS II/IV and BCS III molecules; approved/ marketed drugs and New Molecular Entities (NMEs). **Therapeutic Areas:** Cancer, Immune System, Cardiovascular, CNS, GI, Infectious Diseases, Endocrinology/Metabolic, Inflammation and Tissue Repair. **Regulatory Filings:** IND, ANDA, 505 (b) (2), NDA.

Academic Experience: Teaching and Research Assistant, Postdoctoral Fellow, Associate Research Scientist, Adjunct Assistant Professor of Biochemistry, Adjunct Associate Professor of Pharmaceutics, Professor in-Charge/Instructor of special short courses, Affiliate Associate Professor and Professor of Biopharmaceutical Sciences. Delivered lectures in physical chemistry, biochemistry, pharmaceutics and drug delivery, biotechnology, nanotechnology, entrepreneurship and R&D management. Advisor to academic inventors and founders of university spin-off companies.

Management Experience: Scientific leader and seasoned executive and experienced consultant with excellent organization, interpersonal and communication skills. Results oriented, resourceful and able to interface with the right people/groups both internally and externally to achieve timely results. Timely and focused planning and execution with problem-solving skills and assertiveness in decision making. **Responsibilities:** Founder and Principal, President, Biopharmaceutical & Drug Delivery Consulting, LLC, Vice President of R&D, Director of Research, Section Head, Team Leader/Project Manager in the areas of Discovery Research, Technology and Intellectual Property Development and Management, and Product Development (formulation and method development and validation, scale-up and manufacturing and technology transfer). Developed and managed research and development collaborations and contracts with major universities, big pharma, biotech/drug delivery companies and contract research organizations.

Publications/Patents : 30 original research papers, 1 Commentary, 13 review articles/book chapters, 2 theme issues editor, 3 interview publications, 1 professional development article, 20 poster presentations, 103 invited talks, 17 US Patents (6,008,192; 6,458,373; 6,479,540; 6,660,286; 6,667,048; 8,241,664;8,481,084; 8,492,369;8,536,650; 8,778,916; 8,778,917, 8,828,428, 10,245,273; 10,307,441, 10,463,689, 11,179,402, 11,179, 403), 4 European Patents (1871384,1460992, 2056835,2167069), 17 WO patents (93/02664, 93/02665, 94/08603, 94/08605, 94/08610, 94/19000, 94/19001, 94/19003, 95/08986, 98/40051, 03/047494, 03/047493, 03/057128, 03/057193, 06/113505, 07/117556A2,15/100406), 5 US Patent Applications (US20080317844, US2007/0224293/ 0231412,0281025, US2011/0086069) and 2 other (AU 02/9482601 and US 03/087954). Editorial board member and referee for peer-reviewed journals and invited speaker in 103 presentations at national and international scientific and business meetings. Serves as Expert Witness (consulting and testifying expert) in patent litigation and other pharmaceutical cases.

Professional Associations and Honors: American Chemical Society, Controlled Release Society and American Association of Pharmaceutical Scientists (AAPS). AAPS Fellow, Past Chair of the Formulation Design and Development (FDD) Section, the Lipid-Based Drug Delivery Systems Focus Group and the Nanotechnology Focus Group of AAPS. Member spotlight in the April 2015 issue of AAPS News Magazine. Organizer/Chair/Moderator/Speaker, national and international biomedical, pharmaceutical and nanotechnology conferences, special workshops and short courses. Advisory Board member of university spin-offs and contract development and manufacturing organizations. Editor, AAPS Open journal. Recipient of various awards and recognitions.

EDUCATION AND WORK EXPERIENCE

Education

- 1983 - 1985 **Postdoctoral Fellowship, Pharmacology and Cancer Research, Yale University**, Department of Pharmacology and Cancer Center , School of Medicine, New Haven, Connecticut.
- 1977 - 1983 **Ph.D, Biochemistry (Physical), Brown University**, Chemistry Department Providence, Rhode Island. Thesis Title: "*Physical Properties of Long-Chain Fatty Acyl-CoAs.*" Advisor: Professor Joseph M. Steim.
- 1973 - 1977 **University Diploma (B.S.), Chemistry, National and Kapodistrian University of Greece**, Athens, Greece.

Research and Development Interests/Areas of Involvement

Preformulation: API salt selection, cocrystal and polymorph screening, solubility studies in aqueous solutions as a function of pH and in biorelevant media, API excipient compatibility studies.

Parenteral drug development: small molecules and biologics (peptides/proteins, vaccines, nucleic acids) using liquid and lyophilized formulations, solutions, suspensions and nanosuspensions, liposomes, micelles, emulsions, and other lipid and polymeric nanoparticles.

Topical drug development: solutions, liposomes, emulsions, creams, gels, foams, ointments shampoos and lotions.

Oral formulation development of BCS II, III and IV, small molecules and macromolecules (peptides/proteins) using enabling drug delivery technologies to improve drug solubility and/or intestinal permeability. Oral Dosage Forms: *liquid, aqueous and non-aqueous* (solutions, suspensions, emulsions, self-emulsifying drug delivery systems, such as SEDDS/SMEDDS/SNEDDS), *semi-solid* using high m.p. lipid excipients filled into a hard or soft gelatin capsules; *solid*: tablets and capsules, immediate, sustained and controlled release using multiparticulate dosage forms such as granules and pellets.

Early formulation development with drug discovery compounds to improve drug solubility and/or permeability limitations for preclinical toxicology and Pharmacokinetic (PK) Studies and Proof-of-Concept (POC) studies in humans.

Life cycle management strategies and product line extensions with marketed drugs.

Particle Engineering in API and Drug Product Design; Combination drug products.

Pharmaceutical applications of nanotechnology.

Sustained and Controlled release technologies and dosage forms.

Generic drug development, particularly with branded generics and 505 (b) (2) filing.

Processing and manufacturing aspects of drug formulations (process development, validation and technology transfer), test methods and specifications and strategies to address physical and chemical stability issues for the drug substance and drug product.

Functional excipient development and qualification (DMF Type IV); novel excipients for pharmaceutical development and new uses of pharmaceutical excipients.

Lipid- and/or polymer-based micro- and nanoparticulate systems for targeted drug delivery and controlled release.

Development of lipidic and polymeric drug complexes and conjugates for oral and parenteral administration.

QbD applications in drug formulation and process development and optimization.

Experience

Industrial Research & Development

2005 - present

Founder and Principal/President, Biopharmaceutical & Drug Delivery Consulting, LLC Gurnee, Illinois (website: www.bpddc.com)

Areas of Consulting: Drug product and drug delivery technology development. Chemistry, Manufacturing and Controls (CMC) aspects for small molecule and macromolecule drugs (peptides, proteins, vaccines and nucleic acids). Reformulations of marketed drugs and product line extensions. Scientific, strategic and business assessment (due diligence) of drug product candidates and delivery technologies along with in-/out-licensing recommendations. Identifying, structuring and executing milestone-driven research and development collaborations with corporate partners. Biomedical applications of nanomaterials and nanoparticles. Development and qualification of novel excipients and/or new uses of excipients for pharmaceutical development (DMF Type IV). Intellectual property development strategies and assistance with patent filings and expert witness in patent litigation cases. Development and teaching of short courses for industrial and academic parties.

Clients: biotech and pharmaceutical companies, drug discovery and development companies, university spin-offs and start-ups, generic/specialty pharma, animal health companies, nutraceutical, cosmeceutical, chemical and nanotechnology companies, excipient vendors, contract development and manufacturing organizations (CDMOs), academic institutions, management consulting companies, venture capital and other investment firms, patent law firms and expert witness service organizations.

Therapeutic Areas : Cancer, Cardiovascular, CNS, Endocrinology, Infectious Diseases, Inflammation and Tissue Repair, Metabolic Disorders, Cell Therapies and other.

Dosage forms: parenteral/intravenous, small and large volume parenteral solutions, suspensions, emulsions, lipid and polymeric micro- and nanoparticles; polymeric microspheres, amorphous solid dispersions, oral solid (immediate and controlled release), semi-solid and liquid formulations; topical solutions, liposomes, emulsions, gels, creams, foams and ointments.

Current and Past Projects (working with internal R&D and/or external CROs/CMOs)

Assists several early stage drug discovery companies with diverse product portfolios and targeted disease areas on the execution of their business plan and provides technical input and direction on product development particularly as related to drug delivery, formulation and analytical development, in vitro/ in vivo performance evaluations, Chemistry, Manufacturing and Controls (CMC) for regulatory compliance and filings.

Working with a virtual company since 2004, intimately assisted with the development of a proprietary oral lipid-based technology for lymphatic delivery and absorption from the discovery phase to its progression to advanced clinical development and NDA submission of a drug that is marketed in USA as injectable or topical drug product. This new oral drug product (softgel) was approved by the FDA in 2019 and granted 3-year market exclusivity. Co-inventor of the company's intellectual property portfolio and contributor to patent filing and prosecution.

Provides technical guidance to a pharmaceutical company on the development of a combination parenteral drug product.

Assists specialty pharma companies on the CMC aspects of generic and novel formulations of marketed drugs for ANDA and 505(b) (2) filings.

Provided strategic and technical input to a manufacturer of capsule dosage forms using lipid-based systems.

Provided strategic, technical and business development consulting to a vendor of pharmaceutical excipients.

Serves as a consultant and advisor on chemistry, formulation, manufacturing and controls (CMC) aspects of new molecule entities developed by academic institutions and funded by NIH SBIR/STTR grants.

Working with patent attorneys, assists client companies as a technical expert and/or inventor with the drafting of patent applications, responses to patent office actions and other patent prosecution aspects.

Working with patent law firms and expert witness organizations, serves as expert witness in patent litigation cases dealing with pharmaceutical formulations and drug delivery technologies for injectable, oral and topical drug products.

Provides on-site training seminars to interested parties on delivery and formulation development aspects of challenging molecules (small molecules and peptides) for oral, parenteral and topical dosage forms.

Provided strategic and scientific direction to an established chemical company on several healthcare applications of a GRAS nanomaterial, particularly in the areas of infectious diseases and metabolic disorders.

Working with internal and external groups and senior management, timely and effectively addressed formulation development, physical/chemical stability and scale up and manufacturing issues with proprietary new chemical entities, further advancing their clinical development.

Prepared and submitted to senior management of a client company, a technical assessment of an outside developed formulation/drug delivery technology as an in-licensing opportunity.

Assisted a contract research organization that provides analytical and formulation support services with strategic and technical guidance.

Assisted a large diversified company on strategic plans and provided technical direction on product development and commercialization aspects of a new drug delivery technology.

Successfully served as expert witness in patent litigations cases between innovator and/or generic companies on parenteral, oral and topical drug products working on behalf of plaintiff (s) or defendant (s). Number of completed cases: oral (5), parenteral (4), topical (2). Number of ongoing cases (3).

Assisted an investment firm in their due diligence process and acquisition of a privately held biopharma company.

Developed and served as professor in-charge of a new short course for an academic institution on the Formulation and Drug Delivery Applications of Nanoparticles.

Developed and served as instructor of a Biotechnology Laboratory Operational Management short course offered by an academic institution.

2017-present **Smart Health Activator – member of the Ops Team** (Operations Team). A non-profit organization advancing commercialization of biotechnology being developed by Midwest Universities. Assists on due diligence matters for new molecular entities, formulation, delivery and development aspects.

2003 –2004 **Vice President, Research and Development, Morton Grove Pharmaceuticals, Vernon Hills, Illinois.** Reported directly to the President & CEO.

Led all internal and external product development activities in the areas of generic oral liquids, suspensions, syrups, inhalation solutions, nasal sprays and topical formulations (shampoos, lotions). Direct reports included: formulation and analytical method development and validation, process and instrument/computer validation.

Major Accomplishment: Instrumental in revamping the company's R&D efforts and building the team.

2001- 2003 **Vice President, Research & Development (1/01-7/02) and Consultant (8/02-12/02) DOR BioPharma, Inc (formerly ENDOREX Corporation), Lake Forest, Illinois.** Reported directly to the President & CEO.

Major Accomplishments:

Expanded the company's R&D team including outside consultants.

Streamlined resources and focused R&D activities of the company.

Managed R&D collaborations with two major pharmaceutical companies.

Managed contract manufacturing, stability testing and regulatory filings of OrBec™ (oral beclomethasone dipropionate, IR and CR tablet) a Phase II/III drug product for Graft-vs-Host Disease (GVHD) and Grohn's disease.

Led company's vaccine program (tetanus and influenza) using lipid nanoparticle and microparticle formulation approaches along animal immunization studies upon subcutaneous, peroral and nasal administration.

Expanded company's drug delivery platform and intellectual property portfolio. Created 3 new technology platforms: LPM™ (lipid polymer micelles) for enhancing the intestinal absorption of water-soluble drugs/peptides and LPE™/PLP™ (lipid polymer emulsions/polymer lipid particles) for enhancing the solubilization and oral absorption of water-insoluble drugs. Preclinical proof-of-concept of enhanced oral bioavailability has been demonstrated with leuprolide and paclitaxel, respectively.

Primary inventor of four WO patents and presented company's technologies and product portfolio at six national/international meetings and to business and financial communities.

In July of 2002 after the company adapted the implementation of a major restructuring and downsizing plan, served as a consultant of Oradel Systems Inc. a subsidiary of DOR BioPharma to further develop and/or out license these technologies to big Pharma or other drug delivery companies.

1997-2000

Director of Research, SONUS Pharmaceuticals, Bothell, Washington. Reported directly to the President & CEO.

Major Accomplishments:

Established the company's drug delivery program and expanded its technology base and intellectual property portfolio. Created and developed the company's TOCOSOL™ drug delivery technology.

Leading a team of scientists, developed a novel, stable, filter-sterilizable and efficacious injectable nanoemulsion of paclitaxel (TOCOSOL™-Paclitaxel) from idea inception to scale up, preclinical evaluation and initiation of clinical studies.

Made significant contributions to the company's efforts to build research and development collaborations with big pharmaceutical companies.

1995-1997

Section Head, Formulation Development, Pharmaceutical and Analytical Research and Development, Pharmaceutical Products Division, Abbott Laboratories, North Chicago, Illinois.

Major Accomplishments:

Led project activities on formulation development, scale-up and manufacturing of oral liquid solutions, liquid-filled soft gelatin and semi-solid-filled hard gelatin capsule formulations of cyclosporine.

Contributed to the commercialization of a generic cyclosporine formulation from preclinical development to clinical manufacturing and bioequivalency testing along with all necessary material (CMC section) for the ANDA. Gengraf® approved by the FDA on May 15, '00 as cyclosporine capsules, USP (bioequivalent to Novartis Neoral®).

Led prior art search and patent filing strategy on generic cyclosporine formulations that resulted in 2 major patent filings. Major inventor on the Gengraf™ patent (US 6, 008, 192, December 28, 1999).

Key member of a multi-disciplinary Drug Delivery Technology Evaluation Team within the Formulation Center that interfaced with Corporate Licensing and Business Development to evaluate outside developed technologies with potential applications to Abbott's compounds.

1994-1995

Senior Investigator/Team Leader, Pharmaceutical Product Development, Pharmaceutical Technologies, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania.

Major Accomplishment:

Led a project team that developed a Phase I formulation of a water-soluble molecule which in preclinical studies in dogs and primates showed enhanced oral absorption compared to a solution formulation.

1990 -1994

Senior Investigator, Drug Delivery Department, Pharmaceutical Technologies, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania.

Major Accomplishments:

Interfaced between Discovery Programs and Development Project Teams within SmithKline Beecham, to identify early development candidates and address pre-formulation, formulation development and drug delivery issues with various preclinical compounds, development compounds and product line extensions.

Established a drug delivery program and a useful lipid microemulsion database using model and proprietary water-soluble molecules/peptides from idea inception and formulation development to preclinical evaluation for toxicity and oral bioavailability assessment.

Creation of a strong intellectual property portfolio in the area of oral delivery of water-soluble molecules/peptides using microemulsions. Invented and developed (hands-on) lipid microemulsion formulations that significantly improved the oral absorption of poorly absorbed drugs/peptides in animal models..

Led research activities on the feasibility of liposomal and emulsion formulations to improve the efficacy and reduce toxicity of antitumor and antiviral drugs upon parenteral administration and comparison to drug solutions or suspensions.

Provided several technical appraisals/reports on outside developed drug delivery systems/technologies with recommendations for potential licensing.

1988 - 1989

Project Leader/Liposome Technology Development, Lipogen Inc. Knoxville, Tennessee.

Major Accomplishments :

Provided technical and management support of a group of scientists on the development of a homogeneous liposome-based immunoassay which allows rapid qualitative (yes/no), or quantitative detection of a variety of classes of analyte i.e. therapeutic drugs in biological fluids (serum or urine).

Interfaced group's activities to those of the Marketing and Quality Control departments.

Developed a homogeneous liposome-based immunoassay for the detection and quantification of therapeutic drugs and other analytes in biological fluids.

1987-1988

Research Scientist and Senior Research Scientist/Formulations, Lipogen Inc. Knoxville, Tennessee.

Major Accomplishments:

Research and Development in the area of drug delivery systems using liposomes and other lipid-based carriers. Hands-on experience with drug-liposome formulation and physical characterization, lipid-antibody conjugation (immunoliposomes), design and formulation of phospholipid and other lipophilic prodrugs in liposomes, and stability, sterilization and scale-up of liposomal drugs.

Developed a lipid admixture for the solubilization of lipophilic and other hydrophobic compounds that can be administered parenterally or orally.

Liposome formulation and characterization, kinetic and thermodynamic studies of a homogeneous liposome-based immunoassay.

As a principal investigator, prepared and submitted to NIH two Small Business Innovation Research (SBIR) Phase I grants, on a) Formulation and Antitumor Activity of Lipophilic Methotrexate and, b) Target-Specific Delivery of Lipophilic Anticancer Drugs. Both were highly rated but not approved for funding.

1976

Industrial Internship, Kyknos Canning Company, Nafplion, Greece.

Work involved chemical analysis of canned fruits and vegetables such as acidity, solid content and other quality tests.

Academic Research & Teaching

2014 – 2016

Affiliate Professor of Biopharmaceutical Sciences, Roosevelt University, College of Pharmacy, Schaumburg, Illinois.

Member of the Biopharmaceutical Sciences Research Council.

2012-2013

Affiliate Associate Professor of Biopharmaceutical Sciences, Roosevelt University, College of Pharmacy, Schaumburg, Illinois.

Member of the Biopharmaceutical Sciences Research Council.

2007-2009 **Professor in-charge, University of Wisconsin, School of Pharmacy, Extension Services in Pharmacy.**

Coordinator and co-instructor of the annual short course on “Nanoparticles: Applications in Formulation and Drug Delivery”.

1998 - 2000 **Associate Professor (Affiliate), Department of Pharmaceutics, University of Washington, Seattle, Washington.**

Co-instructor in a Pharmaceutical Biotechnology course and career mentor for graduate students. Research collaborations in drug transport and delivery.

1987- 1989 **Assistant Professor (Adjunct), Biochemistry Department, University of Tennessee, Knoxville, Tennessee.**

Co-instructor in a physical chemistry course (graduate level). Topics covered: lipid and membrane dynamics, biological spectroscopy (NMR, EPR, IR and Raman) and liposome technology.

1985 - 1987 **Associate Research Scientist, (Equivalent to Assistant Research Professor), Department of Pharmacology and the Comprehensive Cancer Center, Yale University School of Medicine, New Haven, Connecticut.**

Research focused on the interaction of anthracyclines with lipid bilayers using Differential Scanning Calorimetry, as well as on size characterization of liposomes using Sedimentation Field Flow Fractionation, Electron Microscopy and Gel-Filtration.

1983 - 1985 **Postdoctoral Fellow, Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut.**

Research focused on: a) adriamycin-induced fusion of liposomes using EPR-spin-labelling, DSC, and Electron Microscopy; b) location of anthracyclines in lipid bilayers by paramagnetic quenching studies; and c) spin-trapping studies of hydroxyl and superoxide free radicals generated by the bioactivation of anticancer antibiotics.

1978 - 1980 **Research Assistant, Brown University, Providence, Rhode Island.**

Thesis research on the physical properties of long-chain fatty acyl-CoAs using Surface Tension, Conductivity, Fluorescence and Analytical Ultracentrifuge. Early work involved enzymatic studies with membrane-bound acyltransferase in a cell-free system to understand how the activity of the enzyme is controlled by the physical state of the lipid bilayer.

1977 - 1983 **Teaching Assistant, Chemistry Department and Division of Biology and Medicine, Brown University, Providence, Rhode Island.**

Assisted in the teaching of Physical, Organic Chemistry and Biochemistry. Responsibilities included lectures on concepts and techniques pertaining to laboratory experiments, and preparation and supervision of laboratory sections and evaluation of student progress by grade assignment.

1976-1977 **Teaching Assistant, Inorganic Chemistry Department, Athens University, Athens, Greece.**

Duties included preparation and supervision of laboratory sections.

1977 **Part-time Teacher in Chemistry, Saint John Institute, Limassol, Cyprus.**

Preparation of high school students for university entrance examinations (G.C.E. level).

Special Skills

Technical

In depth-knowledge of the formulation and drug delivery science. Core competency: physical chemistry and biopharmaceutics of drug delivery systems with research and development expertise in lipid-based systems.

Product development experience (formulation, analytical and process development and manufacturing) of parenteral, oral and topical formulations.

Working knowledge of colloid and surface chemistry techniques, spectroscopic and bioanalytical methods, lipid and membrane biochemical and biophysical methodologies.

Computer skills : MacIntosh and IBM/PC using several programs, such as, Sigma Plot, Prism, Microsoft Office (Word, Excel, Project and Power Point).

Management

Supervisory and Project Management skills. The background of people supervised include: chemists, chemical engineers, biochemists, biologists and pharmacists at a B.Sc, M.Sc and Ph.D levels, as well as, undergraduate and graduate students in the aforementioned disciplines. Experienced in both line and matrix management. Proactive and coaching management style. Results oriented with excellent organization and communication skills.

Networking skills . Ability to interface with various levels of management and groups both internally and externally and achieve results working with multiple teams/disciplines.

Honors and Awards

9/73 - 6/77 Fellowship for Academic Excellence, National Fellowship Foundation of Greece.

9/84 - 9/85 Brown-Coxe Postdoctoral Fellowship, Yale University School of Medicine.

6/85 - present Invited reviewer of research papers and review articles published in various Biochemical, Pharmaceutical and Medical Journals.

1994- present Member of the planning committee of the Annual Industrial Pharmaceutical Research and Development (June Land O' Lakes) Pharmaceutical Conference.

1997 Chair of the June '97 Land O' Lakes Pharmaceutical Conference on "**Challenges and Prospects in the Design and Development of Oral Controlled Release Products**", June 2-6, 1997, Devil's Head Lodge-Merrimac, WI.

2002-2003	Scientific Advisory Board member of the conference on Peptide and Protein Formulation Strategies for Drug Delivery and Development organized by the Institute of International Research.
2003	Chair, Pre-conference Symposium on “Identifying Opportunities and Overcoming Challenges in Oral Protein and Peptide Delivery” of the 2 nd IIR <i>Protein & Peptide Formulation Strategies for Drug Development and Delivery</i> , March 31- April 2, 2003, Boston, MA.
2003	Invited Theme Issue Editor “Advances in Lipid-Based Drug Solubilization and Targeting” <i>Adv. Drug Del. Rev.</i> 56(9) 7 May, 2004.
2006 - 2008	Chair, Lipid-Based Drug Delivery Systems Focus Group of AAPS.
2006	Co-Chair, 2006 BIO Entrepreneurial Boot Camp for Chief Scientific Officers and Academic Researchers, April 8-9, Chicago, Illinois.
2007	Co-Chair, AAPS Workshop “Effective Utilization of Lipid-Based Systems for Enhancing the Delivery of Poorly Soluble Drugs: Physicochemical, Biopharmaceutical and Product Development Considerations” , March 5-6, 2007, Bethesda, MD.
2007	Co-chair, iiBIG Conference “New Directions for Drug Delivery” , October 29-30, 2007, Las Vegas, NV.
2007-2009	Coordinator and Professor in-charge, short course “Nanoparticles: Applications in Drug Formulation and Delivery” , Univ.of Wisconsin, Extension Services in Pharmacy.
2008 - 2009	Past Chair, AAPS Lipid-Based Drug Delivery Systems Focus Group
2009 - 2011	Chair, AAPS Nanotechnology Focus Group .
2010	Elected Fellow of the American Association of Pharmaceutical Scientists (AAPS)
2009-present	Editorial Advisory Board Member, Recent Patents in Drug Delivery and Formulation , Bentham Science Publishers.
2011	Chair, AAPS Drug Delivery Workshop “Emerging Oral Delivery Strategies and Technologies to Enable Biopharmaceutical Performance of BCS II, III and IV Molecules” , April 14-15, 2011, Baltimore, MD.
2011	Co-Chair, 4th Annual Nanotechnology Symposium , Sullivan University, College of Pharmacy, September 23-24, 2011, Louisville, KY.
2012	Chair, 47 th AAPS Arden House Conference “Nanoscience in Pharmaceuticals: Translating Fundamental Understanding to Practical Application in Drug and Device Development” , March 11-14, 2012, The Thayer Hotel, West Point, NY.
11/2012-11/2013	Vice Chair, AAPS Formulation Design and Development (FDD) Section of AAPS.
11/2013-11/2014	Chair-Elect, AAPS Formulation Design and Development (FDD) Section of AAPS.

- 2013 Chair, Program Committee, **Drug Discovery and Development Track, BIO2013** International Convention, April 22-25, 2013, Chicago, IL.
- 2012-present Advisory Committee Member, Nanotechnology Employment, Education and Economic Development, Oakton Community College, Oakton, IL.
- 2013 Organizer and Co-Chair, Sort Course on “**Quality Control Aspects of Nanoparticulate Dugs: Manufacturing, Characterization and Regulatory Considerations**”, Nov. 10, 2013, 2013 AAPS Annual Meeting, San Antonio, TX.
- 2013 Chair, **3rd International Conference and Exhibition on Pharmaceutics & Novel Drug Delivery Systems (Pharmaceutica-2013)**, OMICS Group, April 8-10, 2013, Northbrook, IL.
- 2014 Chair, **4th International Conference and Exhibition on Pharmaceutics & Novel Drug Delivery Systems (Pharmaceutica-2014)**, OMICS Group, March 24-26, 2014, San Antonio, TX.
- 11/2014-10/2015 Chair, Formulation Design and Development (FDD) Section of AAPS.
- 7/28/2015 2016 AAPS Annual Meeting Jamboree Enterprise Award Recipient.
- 8/2015 – 4/2021 Associate Editor and Editor, AAPS Open Journal.
- 10/26/2015 Formulation Design and Development (FDD) Section Chair and Leadership Award, American Association of Pharmaceutical Scientists (AAPS).
- 2018 Chair, **12th World Drug Delivery Summit**, Annual America Congress Organization, September 24-26, 2018, Chicago, Illinois.
- 2021 **Recipient of the 2021 International Pharmaceutical Excipients Council (IPEC) Foundation Henk de Jong Industrial Research Award** for outstanding achievements in Excipient Innovation and Research.

Professional Organizations

Past member of the American Biophysical Society, American Association for Cancer Research, American Association for the Advancement of Science and the New York Academy of Sciences, American Chemical Society and the Controlled Release Society. Active member of the American Association of Pharmaceutical Scientists and BIO/iBIO.

Languages

Native is Greek, fluent in English, some knowledge of French.

Recreational Activities

Strong interest in Byzantine art and music. Enjoys mount hiking, bicycling and sports both as spectator and participant.

References

Available upon request.

PUBLICATIONS, PRESENTATIONS AND PATENTS

Original Research Papers

1. Panayiotis P. Constantinides and Joseph M. Steim (1985) " **Physical Properties of Fatty Acyl-CoAs: Critical Micelle Concentrations, Micellar Size and Shape** " *J. Biol. Chem.* 260, 7573 - 7580.
2. Panayiotis P. Constantinides and Joseph M. Steim (1986), " **Solubility of Palmitoyl-CoA in Acyltransferase-Assay Buffers Containing Magnesium Ions**" *Arch. Biochem. Biophys.* 250, 267 - 270.
3. Panayiotis P. Constantinides and Joseph M. Steim (1988) " **Micellization of Fatty Acyl CoA Mixtures and Its Relevance to the Fatty Acyl Selectivity of Acyltransferases**" *Arch. Biochem. Biophys.* 261, 430 - 436.
4. Chris A. Pritsos, Panayiotis P. Constantinides, Thomas R. Tritton, David C. Heimbrook and Alan C. Sartorelli (1985) " **Use of High Performance Liquid Chromatography to Detect Hydroxyl and Superoxide Radicals Generated from Mitomycin C** " *Anal. Biochem.* 150, 294 - 299.
5. Panayiotis P. Constantinides, Naoyoshi Inouchi, Thomas R. Tritton, Alan C. Sartorelli, and Julian M. Sturtevant (1986) " **A Scanning Calorimetric Study of the Interaction of Anthracyclines with Neutral and Acidic Phospholipids Alone and in Binary Mixtures** " *J. Biol. Chem.* 261, 10196 - 10203.
6. Panayiotis P. Constantinides, Thomas R. Tritton, and Alan C. Sartorelli (1988), " **Interaction of Adriamycin with Single and Multibilayer Dipalmitoylphosphatidylcholine Vesicles: Spin-labelling and Calorimetric Study** " *J. Liposome Res.* 1, 35 - 62.
7. Robert Dreyer, Edward Hawrot, Alan C. Sartorelli and Panayiotis P. Constantinides (1988) " **Sedimentation Field Flow Fractionation of Fused Unilamellar Vesicles: Comparison with Electron Microscopy and Gel Filtration** " *Anal. Biochem.* 175, 433 - 441.
8. Panayiotis P. Constantinides, Naoyoshi Inouchi, Alan C. Sartorelli and Julian M. Sturtevant (1989) " **Interaction of Adriamycin and N-Trifluoroacetyladiamycin-14-valerate with Cardiolipin-Containing Lipid Bilayers** " *J. Liposome Res.* 1, 245 - 260.
9. Panayiotis P. Constantinides, Lily Ghosaini, Naoyoshi Inouchi, Shinichi Kitamura, Ramakrishnan Seshadri, Mervyn Israel, Alan C. Sartorelli and Julian M. Sturtevant (1989) " **Interaction of N-Alkylanthracyclines with Lipid Bilayers: Correlations Between Partition Coefficients, Lipid Phase Distributions and Thermotropic Behavior** " *Chem. Phys. Lipids* 51, 105 - 118.
10. Panayiotis P. Constantinides, Yan Yan Wang, Thomas G. Burke, and Thomas R. Tritton (1990) " **Tranverse Location of Anthracyclines in Lipid Bilayers: Paramagnetic Quenching Studies** " *Biophys. Chem.* 35, 259-264.
11. Bruce Babbitt, Lisa Burtis, Patrick Dentinger, Panayiotis Constantinides, Larry Hillis, Barbara McGill and Leaf Huang (1993) " **Contact-Dependent, Immune-complex-Mediated Lysis of Hapten-Sensitized Liposomes**" *Bioconjugate Chem.* 4, 199-205.

12. Panayiotis P. Constantinides, Jean-Paul Scalart, Cindy Lancaster, Joseph Marcello, Gary Marks, Harma Ellens and Philip Smith (1994) **"Formulation and Intestinal Absorption Enhancement Evaluation of Water-in-Oil Microemulsions Containing Medium-Chain Glycerides "** *Pharm. Research* 11(10), 1385-1390.
13. Panayiotis P. Constantinides, Cindy M. Lancaster, Joseph Marcello, D. Chiossone, Donald Orner, Ismael Hidalgo, Philip L. Smith, Ani B. Sarkahian, Seang H. Yiv and Albert J. Owen (1995) **"Enhanced Intestinal Absorption of an RGD Peptide from Water-in-Oil Microemulsions of Different Composition and Particle Size"**, *J. Control. Rel.*, 34, 109-116.
14. Panayiotis P. Constantinides and Seang H. Yiv (1995) **"Particle Size Determination of Phase-Inverted Water-in-Oil Microemulsions Under Different Dilution and Storage Conditions"**, *Int. J. Pharm.* 115, 225-234.
15. Panayiotis P. Constantinides, Gus Welzel, Harma Ellens, Philip L. Smith, Sandy Sturgis, Seang H. Yiv and Albert J. Owen (1996) **"Water-in-oil Microemulsions Containing Medium-Chain Fatty Acid/Salts : Formulation and Intestinal Absorption Enhancement Evaluation"** *Pharm. Res.* 13, 210-215.
16. Hung-Yuan Cheng, Cynthia S. Randall, Walter W. Holl, Panayiotis P. Constantinides, Tian-Li Yue and Giora Z. Feuerstein (1996) **"Carvedilol-Liposome Interaction: Evidence for Strong Association with the Hydrophobic Region of Bilayers"**, *Biochim. Biophys. Acta* 1284, 20-28.
17. Panayiotis P. Constantinides and Jean-Paul Scalart (1997) **" Formulation and Physical Characterization of Water-in-Oil Microemulsions Containing Long- versus Medium-Chain Glycerides "** *Int. J. Pharm.* 158: 57-68 (1997).
18. Panayiotis P. Constantinides, Karel Lambert, Alexander K. Tustian, Wenwen Ma, Brian Schneider, Salima Lalji, Bryan Wentzel, Dean Kessler, Dilip Worah and Steven C. Quay (2000) **"Formulation Development and Antitumor Activity Evaluation of a Filter-Sterilizable Emulsion of Paclitaxel"**, *Pharm. Res.* 17 : 175-182.
19. Pavel Gershkovich, Jerald Darlington, Panayiotis P. Constantinides and Kishor M. Wasan (2009) **Inhibition of Intestinal Absorption of Cholesterol by Surface-Modified Nanostructured Aluminosilicate (NSAS) Compounds.** *J. Pharm. Sci.* 98: 2390-2400.
20. Olena Sivak, Jerald Darlington, Pavel Gershkovich, Panayiotis P. Constantinides and Kishor M. Wasan (2009) **Protonated Nanostructured Aluminosilicate Reduces Plasma Cholesterol Concentrations and Atherosclerotic Lesions in Apolipoprotein Deficient Mice Fed a High Cholesterol and High Fat Diet**, *Lipids Health Dis.* Jul 28; 8 (1) : 30, online publication.
21. G. Xie, T. Nie, G.C. Mackenzie, Y. Sun, L. Huang, N. Ouyang, N. Alston, O.T. Murray, P.P. Constantinides, L. Kopelovich and B. Rigas (2011), **The Metabolism and Pharmacokinetics of Phospho-sulindac (OXT-328) and the Effect of Difluoromethylornithine**, *Br. J. Pharmacol.* 2011 Sep 28. Doi:10.1111/j.1476-5381.2011.01705.x [Epub].
22. George Mattheolabakis, Ting Nie, Panayiotis P. Constantinides and Basil Rigas (2012), **Sterically Stabilized Liposomes Incorporating the Novel Anticancer Agent Phospho-Ibuprofen (MDC-917): Preparation, Characterization and In Vitro/In Vivo Evaluation**, *Pharm. Res.* 29: 1435 - 1443.

23. Chi C. Wong, Ka-Wing Cheng, Gang Xie, Dingying Zhou, Cai-Hua Zhu, Panayiotis P. Constantinides and Basil Rigas (2012), **Carboxyesterases 1 and 2 Hydrolyse Phospho-NSAIDs to Their Pharmacological Activity**, *J. Pharmacol.. Exp. Ther.* 340:422-432.
24. Ting Nie, Chi C. Wong, Niche Alston, Patrick Aro, Panayiotis P. Constantinides and Basil Rigas (2012), **Phospho-Ibuprofen (MDC-917) Incorporated in Nanocarriers: Anticancer Activity In Vitro and In Vivo**, *Br.J.Pharmacol.* 166: 991-1001.
25. K.A.Wing Cheng, Georgios Mattheolabakis, C.C.Wong, Nengtai Ouyang, Liquan Huang, Panayiotis P. Constantinides and Basil Rigas (2012) **Topical Phosphor-Sulindac (OXT-328) Is Effective in the Treatment of Non-Melanoma Skin Cancer**, *Int. J. Oncol.* 41: 1199-1203.
26. C. Zhu, K.W.Cheng, N. Ouyang, L. Huang, Y. Sun, P.P.Constantinides and B. Rigas (2012), **Phosphosulindac (OXT-328) Selectively Targets Breast Cancer Stem Cells In vitro and in Human Breast Cancer Xenografts**. *Stem Cells*, May 31, 2012, doi: 10.1002/stem.1139 [E-pub].
27. G.Xie, C.C.Wong, K.W.Cheng, L. Huang, P.P.Constantinides and B. Rigas (2012) **Regioselective Oxidation of Phospho-NSAIDs by Human Cytochrome P450 and Flavin Monooxygenase Isoforms : Implications for Their Pharmacokinetic Properties and Safety**, *Br. J. Pharmacol.* 167: 222-232.
28. G.Xie, C.C.Wong, K.W.Cheng, L. Huang, P.P. Constantinides and B. Rigas (2012) **In Vitro and In Vivo Studies of Phospho-Aspirin (MDC-22)**, *Pharm Res* 29 : 3292-3301.
29. R. Zhu, K.W.Cheng, G. Makenzie, L. Huang, Y. Sun, G.Xie, K.Vrankova, P.P.Constantinides and B. Rigas (2012) **Phospho-Sulindac (OXT-328) Inhibits the Growth of Human Lung Cancer Xenografts in Mice : Enhanced Efficacy and Mitochondria Targeting by its Formulation in Solid Lipid Nanoparticles**, *Pharm Res.* 29 : 3090-3101.
30. George Mattheolabakis, Chi C. Wang, Yu Sun, Carol Ann Amelia, Robert Richards, Panayiotis P. Constantinides and Basil Rigas (2014) **Pegylation improves the pharmacokinetics and bioavailability of small-molecule drugs hydrolysable by esterases : A study of phosphor-ibuprofen**, *J. Pharmacol. Exp. Ther.* 351: 61-66.

Commentaries

1. Panayiotis P. Constantinides, Subhashis Chakraborty and Dali Shukla, **Considerations and Recommendations on Traditional and Non-traditional Uses of Excipients in Oral Drug Products**. AAPS Open (2016) 2(1), 1-6 DOI 10.1186/s41120-016-0004-3.
2. Panayiotis P. Constantinides, **Join the Dialogue: Do We Need an Excipient Classification System Based on Their Traditional and Non-Traditional Uses in Drug Products?** AAPS Blog Article posted on July 14, 2016.

Review Articles/Book Chapters/Book Reviews

1. Panayiotis P. Constantinides (1995) **"Lipid Microemulsions for Improving Drug Dissolution and Oral Absorption: Physical and Biopharmaceutical Aspects"**, *Pharm. Res.* 12: 1561-1572.

2. Panayiotis P. Constantinides and Ron Liu (2000) **“Micellization and Drug Solubility Enhancement”** in *Water-Insoluble Drug Formulation* (Liu, R. Ed.), Chapter 9, pp. 213-277, Interpharm Press Inc., Denver, Colorado.
3. Panayiotis P. Constantinides (2000) **“Self-Emulsifying Drug Delivery Formulations in the 21st Century: Challenges and Opportunities”** in *Controlled Drug Delivery: Designing Technologies for the Future* (K. Park and R.J. Mersy, Eds), ACS Symp. Series 752, 284 – 296.
4. Panayiotis P. Constantinides and Kishor M. Wasan (2004) **“Advances in Lipid-Based Drug Solubilization and Targeting”**, in *Advances in Lipid-Based Drug Solubilization and Targeting* (Constantinides, P.P. and Wasan, K. Eds), *Adv. Drug Del. Rev.*, **56** (9) pp. 1239-1240.
5. Panayiotis P. Constantinides, Alex Tustian and Dean Kessler (2004) **“Tocol Emulsions for Drug Solubilization and Parenteral Delivery”** in *Advances in Lipid-Based Drug Solubilization and Targeting* (Constantinides, P.P. and Wasan, K. Eds), *Adv. Drug Del. Rev.*, **56** (9) pp. 1243-1255.
6. Panayiotis P. Constantinides, Jihong Han and Stanley S. Davis (2006) **“Advances in the Use of Tocols as Drug Delivery Vehicles”**, *Pharm. Res.* 23 (2) 243-255.
7. Panayiotis P. Constantinides and Kishor M. Wasan (2007) **“Lipid Formulation Strategies for Enhancing Intestinal Transport and Absorption of P-glycoprotein (P-gp) Substrate Drugs: In vitro/In vivo Case Studies”**, *J. Pharm. Sci.* **96** (2) 235-248.
8. Panayiotis P. Constantinides, Mahesh Chaubal and Robert Shorr (2008) **“Advances in Lipid Nanodispersions for Parenteral Drug Delivery and Targeting”**, theme issue on *Lipid-Based Systems for Enhanced Delivery of Poorly Soluble Drugs* (Christopher J.H. Porter, Kishor M. Wasan and Panayiotis P. Constantinides, Editors) *Adv. Drug Del. Rev.* **60**, pp. 757-767.
9. Panayiotis P. Constantinides (Book Review). **Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery**. Kishor M. Wasan (Ed.), Wiley-Interscience 2007. *Drug Dev. Ind. Pharm.* (2008) 34(5): 558.
10. Navdeep Kaur, Ashwini Gadre, Panayiotis P. Constantinides and Yashwant Pathak (2010) **Nanomedicine: Trends and Perspectives on Technologies and Products**, in *Advances in Nanotechnology and Applications*, Vol. 2, Center for Nanotechnology, Education, Research and Applications, Sullivan University, College of Pharmacy, Louisville, KY.
11. Panayiotis P. Constantinides (2011) **Advances in Nanotechnology and Commercialization Perspectives**, Foreword in *Advances in Nanotechnology and Applications*, Vol. 3, Center for Nanotechnology, Education, Research and Applications, Sullivan University, College of Pharmacy, Louisville, KY.
12. Roy Haskell, Panayiotis P. Constantinides and Duxin Sun **“Perspectives in Pharmaceutical Nanotechnology”**, cover article, AAPS News Magazine January 2012.
13. George Mattheolabakis, Basil Rigas and Panayiotis P. Constantinides (2012), **Nanodelivery Strategies in Cancer Chemotherapy: Biological Rationale and Pharmaceutical Perspectives**, *Nanomedicine* 7 (10): 1577-1590.

14. Liu Changxiao, Panayiotis P. Constantinides, Yazhuo, Li (2014) **R&D in Drug Innovation: Reflections from the 2013 Bioeconomy Conference in China, Lessons Learned and Future Perspectives**, *Acta Pharmaceutica Sinica B*, 4 (2) : 112-119.

Interview Publications

1. **Oral Drug Delivery Technologies: Tackling Clinical and Commercial Challenges**", Deborah Erickson, *Fierce Pharma*, March 2012.
2. **Nanoparticles : A Look Forward** technical retrospective, a look ahead at challenges and opportunities for the development of nanoparticle drug delivery systems, Amy Ritter (Moderator), *BioPharm International*, 25 (6) : 28 (2012).
3. **Nanoformulations**, Q&A session with Biopharmaceutical & Drug Delivery Consulting, LLC moderated by Amy Ritter, *Pharm Tech*, July 2012.
4. **IPEC Foundation Recognizes Panayiotis P. Constantinides**, a recipient of the 2021 IPEC Foundation Henk de Jong Industrial Research Achievement for Excipient Technology Award. Published in the *February 2022 Issue of IPEC Americas Insider*.

Professional Development Articles

1. Panayiotis P. Constantinides, **Building a Consulting Business : A Practitioner's Perspective**, AAPS News Magazine May 2016, pp. 31-34.

Abstracts/Poster Presentations

1. Panayiotis P. Constantinides, Naoyoshi Inouchi, Thomas R. Tritton, Alan C. Sartorelli, and Julian M. Sturtevant (1986) "**Comparative Study of the Interaction of Anthracyclines with Lipid Bilayers Using High Sensitivity Differential Scanning Calorimetry** " *Biophysical J.* **49**, 511. Presented at the 30th Annual Biophysical Society Meeting, February 9-13, 1986, San Francisco, California.
2. Panayiotis P. Constantinides, Naoyoshi Inouchi, Alan C. Sartorelli, and Julian M. Sturtevant (1986) " **Interaction of Anthracyclines with Cardiolipin-Containing Neutral and Acidic Liposomes Using High Sensitivity Differential Scanning Calorimetry** " *Delivered at the 41st Calorimetry Conference, August 17-22, 1986, Somerset, New Jersey, Abstract No. 79.*
3. Panayiotis P. Constantinides, Lily Ghosaini, Naoyoshi Inouchi, Shinichi Kitamura, Ramakrishnan Seshadri, Mervyn Israel, Alan Sartorelli, and Julian M. Sturtevant (1987) " **Interaction of N-Alkylanthracyclines with Lipid Bilayers Using High Sensitivity Differential Scanning Calorimetry** " *Biophysical J.* **51**, 239. Delivered at the 31st Annual Biophysical Society Meeting, February 22-26, 1987, New Orleans, Louisiana.
4. Panayiotis P. Constantinides, Jean-Paul Scalart, C. Lancaster, J. Marcello, G. Marks, H. Ellens and P. Smith (1993), "**Water-in-Oil Microemulsions Containing Medium-Chain Glycerides: Formulation and Absorption Enhancement Evaluation in the Rat**" *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* **20**: 184-185. Delivered at the 20th International Symposium of the Controlled Release Society, July 25-28, 1993, Washington, DC.
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- Miller-Stein, Richard Simpson, Fadia Ali and James Samanen (1994) **"Enhancement of RGD Peptide Oral Activity with a Water-in-Oil Microemulsion"**. Presented at the Gordon Conference on Chemistry and Biology of Peptides, February 13-17, 1994 , Ventura, CA.
6. Panayiotis P. Constantinides, Patrick Dentinger and Leaf Huang (1994), **"Incorporation of Lipophilic Drugs into Liposomes from Lipid : Ethanol Admixtures and Comparisons with Conventional Liposomes"**. *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* 21, 501-50, June 27-30, 1994, Nice, France.
 7. Panayiotis P. Constantinides, Cindy Lancaster, J. Marcello, D. Chiossone, D. Orner, I. Hidalgo, A. Sarkahian, S. H. Yiv, A. B. Owen and P. L. Smith, (1994) **"Oral Absorption Enhancement of an RGD Peptide from Water-in-Oil Microemulsions of Different Composition and Particle Size"**. *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* 21, 62-63, June 27-30, 1994, Nice, France.
 8. Panayiotis P. Constantinides and Seang H. Yiv, (1994), **" Particle Size Determination of Phase-Inverted Water-in-Oil Microemulsions Under Different Dilution and Storage Conditions"** *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* 21, 766-767. June 27-30, 1994, Nice, France.
 9. Gary. J. Marks, Gus. Welzel, Philip. L. Smith, Panayiotis .P. Constantinides and H. Ellens, (1995), **"Bioavailability Enhancement of Hydrophilic Molecules by Medium-Chain Glycerides in the Rat"**. Presented at the *Intern. Symp. Control. Rel. Bioact. Mater* 22, July 30-August 4, 1995, Seattle, WA.
 10. Panayiotis P. Constantinides, Gus Welzel, Harma Ellens, Philip L. Smith, Sandy Sturgis, Seang H. Yiv and Albert J. Owen (1996) **"Water-in-oil Microemulsions Containing Medium-Chain Fatty Acid/Salts : Formulation and Intestinal Absorption Enhancement Evaluation "**. Presented at the annual meeting of the American Association of Pharmaceutical Scientists, October 27-31, 1996, Seattle, WA.
 11. Panayiotis P. Constantinides, Karel Lambert, Alexander K. Tustian, Wenwen Ma, Brian Schneider, Salima Lalji, Bryan Wentzel, Dean Kessler, Dilip Worah and Steven C. Quay, **"Reduced Toxicity and Improved Efficacy of Paclitaxel Incorporated in Oil-in-Water Emulsions"** presented at the AAPS Annual Meeting, November 15-19, 1998, San Francisco, California.
 12. Panayiotis P. Constantinides, Dean Kessler, Alexander Tustian, Karel Lambert and Eric A. Rowinsky **" Antitumor Activity of QW8184, an Injectable Paclitaxel Emulsion, and Taxol® in the B16 Melanoma and IGROV-1 Ovarian Tumor Xenograft Models in Mice"** presented at the AACR-NCI-EORTC International Conference on *"Molecular Targets and Cancer Therapeutics: Discovery, Development and Clinical Validation"*, November 16-19 , 1999, Washington, DC.
 13. Eun-Hyun Jang, Likun Liang and Panayiotis P. Constantinides, **"Factors Controlling the In Vitro Release of Rhodamine-Dextran from Polymerized Liposomes in Simulated Intestinal Fluid"**, 29th Annual Meeting and Exposition of the Controlled Release Society, July 20-25, 2002, Seoul, Korea.
 14. Panayiotis P. Constantinides, Likun Liang, Eun-Hyan Jang, David J. Fast, Liangxiu He, Lanlan Li and Kayode Opeifa **"Enhanced Intestinal Absorption of LHRH and Leuprolide In The**

Rat from Lipid Polymer Micelles", 29th Annual Meeting and Exposition of the Controlled Release Society, July 20-25, 2002, Seoul, Korea.

15. Panayiotis P. Constantinides, Likian Liang, David J. Fast, Sumeet Dagar, Liangxiu He, Lanlan Li and Kayode Opeifa **"Bioavailability Enhancement of Leuprolide Upon Intraduodenal Administration in Dogs from Lipid Polymer Micelles (LPM™)"**, 2002 Annual AAPS Meeting and Exposition, November 10 – 14, 2002, Toronto, Canada.
16. Dave J. Fast, Reena Patil, Kevin Bosman and Panayiotis P. Constantinides, **"Lipid Polymer Emulsions (LPE™) Incorporating P-glycoprotein Inhibitors Enhance the Intestinal Absorption of Paclitaxel"**, 2002 Annual AAPS Meeting and Exposition, November 10 – 14, 2002, Toronto, Canada.
17. Jerry W. Darlington and Panayiotis P. Constantinides. **Virus Inactivation by Nanobentonite in Suspended Cells and on Hard Surfaces**. BIO 2007 International Convention, Innovation Corridor Poster Session, May 6-9, 2007, Boston, MA
18. Olena Sivak, Pavel Gershkovich, Jerald Darlington, Panayiotis P. Constantinides and Kishor M. Wasan. **Potential Anti-hyperlipidemic Activity of Nanoscale Aluminosilicate (NSAS) in Rabbits**. 2008 AAPS Annual Meeting and Exposition, November 16-20, 2008 Atlanta, GA
19. Pavel Gershkovich, Olena Sivak, Jerald Darlington, Panayiotis P. Constantinides and Kishor M. Wasan. **Inhibition of Intestinal Absorption of Cholesterol by Novel Aluminosilicates (NSAS) compounds**. 2008 AAPS Annual Meeting and Exposition, November 16-20, 2008 Atlanta, GA.
20. Pavel Gershkovich, Jerald Darlington, Panayiotis P. Constantinides and Kishor M. Wasan. **Protonated Nanoscale Aluminosilicate (NSAS) Reduces Plasma Cholesterol Concentrations and Atherosclerotic Lesion Formation in Apolipoprotein E (ApoE)-Deficient Mice**". 2009 AAPS Annual Meeting and Exposition, November 8-12, 2009, Los Angeles, CA.

Invited Talks

1. Panayiotis P. Constantinides, Jean-Paul Scalart, Joe Marcello, Richard Kirsh and Phil Smith (1991) **"Optimization and Utilization of Microemulsion Delivery Systems for Oral Administration of Peptidergic Drugs"** *2nd Annual SmithKline Beecham Drug Delivery Workshop, June 25-26, 1991, Harlow, UK.*
2. Panayiotis P. Constantinides and Jean-Paul Scalart **"Self-Emulsifying Water-in-Oil Microemulsions in Drug Delivery: Formulation and Physical Characterization"** *First International Conference on Pharmaceutical Science and Technology and the ACS Fine Particle Society, August 24-28, 1993, Chicago, Illinois.*
3. Panayiotis P. Constantinides **"Self-Emulsifying Water-in-Oil Microemulsions in Drug Delivery: Formulation and Oral Absorption Enhancement Evaluation"** *"Emulsion Day" symposium, SmithKline Beecham Consumer Brands, Nov. 1, 1993, Weybridge, UK.*
4. Panayiotis P. Constantinides, **"Intestinal Absorption Enhancement Using Microemulsion Formulations"**, *Second International Symposium on Pharmaceutical Sciences and Technology of the Fine Particle Society, July 25-28, 1994, E. Brunswick, NJ.*

5. Panayiotis P. Constantinides and Seang H. Yiv, "**Particle Size Measurements of Phase Inverted Water-in-Oil Microemulsions**", lead lecture at the *Second International Symposium on Pharmaceutical Sciences and Technology of the Fine Particle Society*, July 25-28, 1994, E. Brunswick, NJ.
6. Panayiotis P. Constantinides, Patrick Dentinger and Leaf Huang, "**Admixture Liposomes Solubilizing Lipophilic Drugs: Characterization and Potential Applications**", *Second International Conference on Pharmaceutical Sciences and Technology of the Fine Particle Society*, July 25-28, 1994, E. Brunswick, NJ.
7. Panayiotis P. Constantinides, "**Formulation Strategies to Improve the Oral Absorption of Poorly Absorbed Drugs**", invited quest seminar at the *Philadelphia College of Textiles and Science*, October 20, 1994 Philadelphia, PA.
8. Panayiotis P. Constantinides, "**Formulation Design/Development Considerations of Multiphase Systems for Parenteral and Oral Drug Delivery**", invited speaker and a member of the organizing committee of the 37th Annual International Industrial Pharmaceutical Research and Development Land O' Lakes Conference on "Multiphase Systems for Parenteral and Oral Drug Delivery: Physical and Biopharmaceutical Aspects", June 5-9, 1995, Merrimac, Wisconsin.
9. Panayiotis P. Constantinides, "**Water-in-oil Microemulsions for Oral Delivery of Drugs/Peptides with High Aqueous Solubility and Low Membrane Permeability**", delivered at the American Chemical Society's "Conference on Formulations and Drug Delivery", October 10-13, 1995, Boston, Massachusetts.
10. Panayiotis P. Constantinides, "**Lipid Microemulsions as a Novel Dosage Form for Poorly Absorbed Drugs**", delivered at the Food and Drug Administration Agency, October 18, 1996, Rockville, Maryland.
11. Panayiotis P. Constantinides, "**Drug Development Aspects with Water-in-Oil Microemulsions for Oral Delivery of Poorly Absorbed Water-Soluble Drugs/Peptides**", delivered at the symposium on *Lipid-based systems for oral drug delivery: Physiological, Mechanistic and Product Development Perspectives*, Nov. 3, 1997 AAPS Annual Meeting, Boston, MA.
12. Panayiotis P. Constantinides, "**Physical and Biopharmaceutical Aspects of Self-Emulsifying Microemulsion Systems for Oral Drug Delivery**", delivered at Pharmacia & Upjohn (Pharmaceutical Development), February 2, 1998, Kalamazoo, Michigan.
13. Panayiotis P. Constantinides, "**Challenges and Opportunities in the Use of Self-Emulsifying Drug Delivery Systems for Oral Drug Delivery and Intestinal Absorption Enhancement**", delivered on March 11, 1999, University of Washington School of Pharmacy, Department of Pharmaceutics and Medicinal Chemistry.
14. Panayiotis P. Constantinides, "**Self-Emulsifying Drug Delivery Systems in the 21st Century : Challenges and Opportunities**", delivered at the ACS Symposium on "*Drug Delivery in the 21st Century*", March 21-23, 1999, Anaheim, California.
15. Panayiotis P. Constantinides, "**Product Development Opportunities with Alternative Drug Delivery Systems for Marketed Chemotherapeutics**", delivered at the IBC Conference on

“Drug Delivery Systems: Strategies for Competitive Advantage”, May 24-25, 1999, Washington, DC.

16. Panayiotis P. Constantinides, **“Lipid Microemulsions in Drug Solubilization and Delivery”**, delivered at the ACS Symposium *“Microemulsions: Properties and Applications”*, August 20 – 21, 2000, Washington, DC.
17. Panayiotis P. Constantinides, Karel J. Lambert, Alex K. Tustian, Salima Lalji and Dean Kessler, **“Stable and Efficacious Filter Sterilizable Tocol Microemulsions- A Case Study with Paclitaxel”**, invited paper at the *Pharmaceuticals 2000* virtual conference (internet based), November 6-10, 2000.
18. Michael S. Rosen and Panayiotis P. Constantinides, **“ Oral Drug/Peptide : Commercial and Technological Challenges”**, delivered at the 6th US-Japan Symposium on Drug Delivery Systems, Dec. 16-21, 2001, Maui, Hawaii.
19. Panayiotis P. Constantinides, **“Emulsion and Micellar Nanoparticles for Oral Drug/ Peptide Delivery”**, delivered at the Gordon Research Conference on Drug Carriers in Medicine & Biology, Feb. 24 – March 1, 2002, Ventura, California.
20. Panayiotis P. Constantinides **“Lipid Microemulsions and Micellar Nanoparticles for Oral Drug/Peptide Delivery”** invited talk at the Particles 2002 International Conference: **Medical/Biochemical, Diagnostic, Pharmaceutical, and Drug Delivery Applications of Particle Technology**, April 20-23, 2002, Orlando, Florida.
21. Panayiotis P. Constantinides **“Lipid Polymer Micelles and Emulsions for Improving Oral Drug/Peptide Absorption”**, presented at the 19th Technology Transfer Forum of the Technology Catalysts, Inc., May 12-14, 2002, Reston, Virginia.
22. Panayiotis P. Constantinides, **“Development of Oral Peptide Formulations Using Lipid-Based Microemulsion and Micellar Delivery Systems”**, delivered at the *Protein & Peptide Formulation Strategies for Drug Development and Delivery* ,pre-conference workshop on Strategies for Formulating Macromolecules for Oral Delivery, August 19-20, 2002, San Francisco, California, presented by the Institute for International Research and Drug Delivery Partnerships.
23. Panayiotis P. Constantinides, Charles Conover, Steven J. Prestrelski and Thomas Tice, panel discussion on **“Managing Intellectual Property During Drug Delivery Partnerships”**, *Protein & Peptide Formulation Strategies for Drug Development and Delivery*, August 19-20, 2002, San Francisco, California.
24. David J. Fast, Reena Patil, Kevin Bosman, Lori-Pokorsky Loy and Panayiotis P. Constantinides, **“Enhancement of Paclitaxel Transport and Intestinal Absorption Using Lipid Polymer Emulsions (LPE™) Incorporating P-glycoprotein Inhibitors”**, *International Symposium on Tumor Targeted Delivery Systems* sponsored by CRS/NCI, September 23-25, 2002, Bethesda, Maryland.
25. Panayiotis P. Constantinides, **“Identifying Opportunities and Overcoming Challenges in Oral Protein and Peptide Delivery”** Pre-conference Symposium chair and introductory talk, 2nd Intern.. Institute of Research (IIR) *Protein & Peptide Formulation Strategies for Drug Development and Delivery*, March 31- April 2, 2003, Boston, MA.

26. Panayiotis P. Constantinides, **“Dispersed Systems in Oral Peptide/Protein Delivery : Microemulsion and Micellar Systems”** invited talk at the Pre-conference Symposium of the 2nd IIR Protein & Peptide Formulation Strategies for Drug Development and Delivery, March 31- April 2, 2003, Boston, MA
27. Panayiotis P. Constantinides, **“Formulation Strategies to Overcome Drug Absorption Barriers Due to Intestinal Efflux Pumps”**, invited talk at the IIR’s Oral Drug Delivery Conference, June 23-24, 2003, Boston, MA.
28. Panayiotis P. Constantinides, **“Overcoming Biological Barriers to the Oral Absorption of Small Molecule and Macromolecular Drugs Using Lipid-Based Systems”**, invited talk at the University of Cyprus, March 31, 2004, Nicosia, Cyprus.
29. Panayiotis P. Constantinides, **“Intravascular and Oral Delivery of the Chemotherapeutic Drug Paclitaxel Using Microemulsifying Lipid Systems “**, invited talk at Hebrew University, April 14, 2004, Jerusalem, Israel.
30. Panayiotis P. Constantinides, **“Advanced Tocol Emulsions and Lipid Polymer Emulsions for Parenteral and Oral Delivery of Poorly Soluble Drugs”**, invited talk at Eastman Chemical, May 14, 2004, Kingsport, TN.
31. Panayiotis P. Constantinides, **“Case Study : Injectable Drug Products”** invited talk at the 2004 June Land O’ Lakes Conference on *“Role of Excipients in Solubility and Bioavailability Enhancement : Current Approaches, Unmet Needs, and Future Directions”*, Merrimac, Wisconsin, June 7-11, 2004.
32. Panayiotis P. Constantinides **“Effective Utilization of Lipid-Based Systems to Enhance Solubility and Bioavailability of Small Molecule and Macromolecule Drugs”**, invited talk at ALZA Corporation/Johnson & Johnson, September 24, 2004, Mountain View, CA.
33. Panayiotis P. Constantinides, **“Scientific and Technological Advances of Nanotechnology”**, moderator and panelist, session on *“Nanotechnology and Drug Therapy”* of the 2004 Marketplace Meeting sponsored by the Illinois Biotech Industry Organization (IBIO), October 25-26, 2004, Chicago, Illinois.
34. Panayiotis P. Constantinides, **“Effective Utilization of Oral Lipid Formulations to Overcome Intestinal Drug Transport and Membrane Permeability Barriers”**, invited talk at the Barnett International Conference on *“Lipid-Based Formulations/Drug Delivery”*, September 29-30, 2004, Philadelphia, PA.
35. Panayiotis P. Constantinides, **“Tocol Emulsions for Drug Solubilization and Parenteral Delivery”**, invited talk at the symposium *“New Developments in Parenteral Lipid-Based Drug Delivery Systems”*, (P. Constantinides and K. Wasan, symposium organizers), 2004 American Association of Pharmaceutical Scientists, Annual Meeting, November 7-11, 2004, Baltimore, MD.
36. Panayiotis P. Constantinides, **“Opportunities and Challenges in the Development of Combination Products of Oral Drugs with P-glycoprotein Limited Absorption”**, invited talked at the Parexel Conference on *“Fixed Combination Product Development”*, March 7-8, 2005, San Diego, CA.

37. Panayiotis P. Constantinides, **“Drug Solubility and Bioavailability Enhancement Using Lipid Emulsion and Micellar Systems”**, invited talk at the University of Kentucky, College of Pharmacy, April 1, 2005, Lexington, KY.
38. Panayiotis P. Constantinides, **“Biopharmaceutical and Pharmaceutical Technology Aspects of Combination Drug Development : Oral Drugs with P-glycoprotein Limited Absorption”**, invited talk at the Parexel’s Conference on *“Combination Product Development : Leveraging the Current Scientific, Regulatory and Legal Environment to Gain Regulatory Approval ”*, June 9-10, 2005, Brussels, Belgium.
39. Panayiotis P. Constantinides, **“Development of Lipid Formulations for Oral Drugs Exhibiting P-glycoprotein Limited Absorption ”**, invited talk at the Chicagoland Pharmaceutical Discussion Group, December, 1, 2005.
40. Panayiotis P. Constantinides, **“Project, Product or Company : A CSO Perspective”**, invited talk at the *BIO 2006 Entrepreneurial Boot Camp for Chief Scientific Officers and Academic Researchers*, Session 4, April 8-9, 2006, Chicago, IL.
41. Panayiotis P. Constantinides, **“Critical Role of Biopharmaceutics in Bridging Product Quality and Product Performance”**, invited talk at the symposium *Challenges and Opportunities on the Critical Path to Lipid-Based Oral Dosage Forms-Assessment of Product Quality, Product Performance and Therapeutic Equivalence”*, Annual AAPS Meeting and Exhibition, October 29-November 2, 2006, San Antonio, TX.
42. Panayiotis P. Constantinides, **“Advances in the Use of Lipid-Based Systems for Parenteral Drug Delivery”**, invited talk at the AAPS Workshop on *Effective Utilization of Lipid-Based Systems to Enhance the Delivery of Poorly Soluble Drug : Physicochemical, Biopharmaceutical and Product Development Considerations* (P.P.Constantinides and C.H. Porter, organizers), March 5-6, 2007, Bethesda, MD.
43. Panayiotis P. Constantinides, **“Overcoming Physicochemical and Biological Barriers to Drug/Peptide Delivery Using Lipid-Based Systems”** invited seminar at the Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, March 13, 2007.
44. Panayiotis P. Constantinides, **“Project, Product or Company : A CSO Perspective”**, invited talk at the *BIO 2007 The Biotechnology Entrepreneurship Boot Camp*, Session 4, May 6-9, 2007, Boston, MA.
45. Panayiotis P. Constantinides, course coordinator and lead faculty on **“Nanoparticles : Applications in Drug Formulation and Delivery”**, University of Wisconsin Extension Services in Pharmacy, May 21-23, 2007, Madison, WI.
46. Panayiotis P. Constantinides, **“Advances and Future Developments in Drug Delivery Nanotechnology”**, invited Workshop A talk, iiBIG conference on *“New Directions for Drug Delivery”*, (co-chaired by Panayiotis P. Constantinides and Mahesh Chaubal), October 29-30, 2007, Las Vegas, NV.
47. Panayiotis P. Constantinides, **“Lipid Formulation Strategies for Enhancing Solubility and Permeability of BCS IV Drugs : In Vitro/In vivo Case Studies”**, invited talk at the symposium *BCS IV Drugs : Develop or Discard*, 2007 AAPS Annual Meeting, Nov. 11- 15, 2007, San Diego, CA.

48. Panayiotis P. Constantinides, moderator and speaker in a Workshop on **“Biomedical Nanotechnology: Progressing from Bench to Clinic to Commercialization”**, iBIO IndEx 2008, Feb. 20, 2008, Chicago, IL.
49. Panayiotis P. Constantinides, course coordinator and lead faculty on **“Nanoparticles : Applications in Drug Formulation and Delivery”**, University of Wisconsin Extension Services in Pharmacy, May 12-14, 2008, Madison, WI.
50. Panayiotis P. Constantinides **“Oral and Injectable Nanoparticles”**, invited talk at the *50th Annual June LOL International Industrial Pharmaceutical R&D Conference “Designing Drug Delivery Systems : Past, Present and Future Opportunities for Treating Our Patients”*, June 2-6, 2008, Merrimac, Wisconsin.
51. Panayiotis P. Constantinides, **“Project, Product or Company : A CSO Perspective”**, invited talk at the *BIO 2008 The Biotechnology Entrepreneurship Boot Camp* , Session 4, June 16-17, 2008, San Diego, CA.
52. Panayiotis P. Constantinides **“Diversity and Versatility of Lipids in Enhancing the Delivery of Drugs: Physicochemical and Biopharmaceutical Aspects”**, session on *Lipids in Pharmaceutics* (A.Tselepis and P.P. Constantinides, co-chairs), 6th Euro Fed Lipid Congress, Sept. 7-10, 2008, Athens, Greece.
53. Panayiotis P. Constantinides **“Scientific and Technological Advances in Nanoparticles for Drug Formulation and Delivery”** and **“Oral Self-Assembled Lipid Nanostructures in Drug Delivery: Physicochemical and Biopharmaceutical Aspects”**, Nanomedicines 08 Intensive Course and Drug Delivery Workshop, Sept. 12-22, 2008, University of Patras, Greece.
54. Panayiotis P. Constantinides **“Formulation Development Considerations for Liquid-Filled Hard Capsules”**, a symposium on *Emerging Technologies: Liquid Fill Hard Capsule Technology in the Pharmaceutical Industry*, AAPS Annual Meeting, November 16-20, 2008, Atlanta, GA.
55. Panayiotis P. Constantinides, **“Advances in Lipid Nanodispersions and Nanoparticles for Non-Oral Drug Delivery and Targeting”** invited keynote talk at the workshop *“Scientific and Technological Advances in the Use of Lipid-Based Drug Delivery Systems for Bioavailability Enhancement and Tissue Targeting”*, March 9-11, 2009, Baltimore, MD.
56. Panayiotis P. Constantinides **“Product Development Considerations on the Use of Nanoparticles in Drug Formulation and Delivery”**, invited talk in the conference *Challenges in Global Product Development: Developing Rugged and Robust Products, Processes and Specifications*, March 31 - April 2, 2009, Bar Ilan University, Tel Aviv, Israel.
57. Panayiotis P. Constantinides **“Nanoparticles : Definitions and Product Development Considerations”**, invited panel talk at the Roundtable *Nanoparticles-Are They Ever Going to Amount to Anything*, 2009 AAPS Annual Meeting, November 8-12, 2009, Los Angeles, CA.
58. Panayiotis P. Constantinides **“Why, When and What Lipid-Based Formulations and Dosage Forms to Consider with BCS II and IV Compounds”**, invited talk at the 2010 June LOL Pharmaceutical Conference on *Science-Driven Drug Product Development Strategies to Achieve Proof of Concept*, June 7-11, 2010, Merrimac, WI.

59. Panayiotis P. Constantinides **“Pharmaceutical Nanoparticulate Systems : Case Studies and Product Development Considerations”**, invited keynote talk at the 3rd Annual Nanotechnology Symposium, September 24-25, 2010, Sullivan University, Louisville, KY.
60. Panayiotis P. Constantinides **“Enhancing Solubility, Intestinal Permeability and Bioavailability with Lipids: Principles and Case Studies with BCS II, III and IV Molecules”**, seminar, November 19, 2010, Cubist Pharmaceuticals, Lexington, MA.
61. Panayiotis P. Constantinides, panelist in the workshop on **“Working with Industry: Designing Your Academic Research for Successful Collaboration: Part I, Basic Sciences Research”**, January 13, 2011, Rush University Medical Center, Chicago, IL.
62. Panayiotis P. Constantinides, organizer and panelist, panel on **“Commercializing Nanobiotechnology: Research, Development, Legal and Investment Perspectives”**, iBIO 2011 IndEx, February 15-16, 2011, Chicago, IL.
63. Panayiotis P. Constantinides **“Improving Poor Biopharmaceutical Properties of Small Molecules and Macromolecules with Lipids: Rationale, Achievements and Challenges”**, invited talk at the 2011 AAPS Drug Delivery Workshop on *Emerging Oral Delivery Strategies and Technologies to Enable Biopharmaceutical Performance of BCS II, III and IV Molecules*, April 14-15, 2011, Baltimore, MD.
64. Panayiotis P. Constantinides **“Product Development Considerations with Targeted Nanotheragnostics”**, invited talk at the symposium on *Targeted Nanotheragnostics : Scientific Achievements and Commercialization Challenges*, 2011 AAPS National Biotechnology Conference, May 16-18, 2011, San Francisco, CA.
65. Panayiotis P. Constantinides **“Solubility and/or Permeability Enhancement Using Lipids: Case Studies”**, invited talk at the 2011 June LOL Pharmaceutical Conference on *Solubility and Bioavailability Enhancement: Product Development Strategies for Classic Challenges*, June 6-10, 2011, Merrimac, WI.
66. Panayiotis P. Constantinides **“Nanoparticle Strategies in Cancer Drug Delivery: Biopharmaceutical Perspectives”**, Plenary Lecture, 4th Annual Nanotechnology Symposium, September 23 - 24, 2011, Sullivan University, Louisville, KY.
67. Panayiotis P. Constantinides **“Pharmaceutical Nanoparticulate Systems: Principles, Case Studies and Product Development Considerations”**, invited speaker by the AAPS Greater Maryland Discussion Group (GMDC), October 11, 2011, University of Maryland, School of Pharmacy, Baltimore, MD.
68. Panayiotis P. Constantinides, organizer, moderator and panelist on **“Solid Self-Emulsified Water-in-Oil Microemulsions, Reverse Micelles and Nanoparticles”**, Roundtable on *Transforming Oral Liquid Lipid Formulations of BCS II, III and IV Molecules to Solid Dosage Forms: Prospects and Challenges*, 2011 AAPS Annual Meeting, October 23-27, 2011, Washington, DC.
69. Panayiotis P. Constantinides **“Pharmaceutical Emulsions and Related Systems for Oral and Topical Administration: Principles, Characterization and Cases Studies”** seminar, December 2, 2011, Merck Consumer Care, Memphis, TN.

70. Panayiotis P. Constantinides **“Pharmaceutical Nanoparticulate Systems: Principles, Case Studies and Product Development Considerations”**, webinar, December 13, 2011 Johnson & Johnson Science Forum/Delivery Technology Update.
71. Panayiotis P. Constantinides **“Lipidic Nanoparticulates : Design and Development Considerations and Case Studies”**, invited talk at the 47th AAPS Arden House Conference *Nanoscience in Pharmaceuticals: Translating Fundamental Understanding to Practical Application in Drug and Device Development*, March 11-14, 2012, The Thayer Hotel, West Point, NY.
72. Panayiotis P. Constantinides, **“Enabling Oral Drug Delivery with Lipids : Trends and Perspectives”** invited talk at the 2012 AAPS Workshop *Lipid-Based Delivery for Improving Drug Absorption : Mechanistic Understanding and Practical Approaches*, April 23-24, 2012, Baltimore, MD.
73. Panayiotis P. Constantinides, **“Parenteral and Oral Lipid Nanodispersions for Small Molecules and Macromolecule Delivery: Biopharmaceutical Considerations and Case Studies”**, invited talk at the symposium *Advances in Lipid-Based Nanoparticulate Systems for Drug and Vaccine Delivery*, CSPS Conference “Modern Therapeutics 2012: Advances in Physiology, Pharmacology & Pharmaceutical Sciences”, June 12-15, 2012, Toronto, Canada.
74. Panayiotis P. Constantinides **“Nanoparticle Technologies in Drug Formulation and Delivery : Design and Development Considerations and Case Studies”**, invited distinguished speaker at the *Innovative Technologies in Healthcare* Global Seminar sponsored by Evonik, March 5-6, 2013, Mumbai, India.
75. Panayiotis P. Constantinides, **“Oral Lipid-Based Systems in Drug Development and Life Cycle Management”** invited quest lecture at VerGo Pharma and India Pharmaceutical Association, March 8, 2013, Verna, Goa, India.
76. Panayiotis P. Constantinides **“Advances in Nano Drugs for Cancer Chemotherapy : Biopharmaceutical Trends and Perspectives and Case Studies”**, keynote talk at the 3rd *International Conference and Exhibition on Pharmaceutics & Novel Drug Delivery Systems (Pharmaceutica-2013)*, OMICS Group, April 8-10, 2013, Northbrook, IL.
77. Panayiotis P. Constantinides, **“Project, Product or Company : A CSO/CTO Perspective”**, invited talk and panelist at the *BIO 2013 Biotechnology Entrepreneurship Boot Camp* , Session 3, April 21-22, 2013, Chicago, IL.
78. Panayiotis P. Constantinides **“Entrepreneurship and Starting a New Business”** panelist in a roundtable on *Biotech Career Transition: Adaptability to Change and Strategies for Success*, (P.P. Constantinides and P. Ramsey, organizers), 2013 AAPS National Biotechnology Conference, May 20-22, 2013, San Diego, CA.
79. Panayiotis P. Constantinides **“The Scientific Basis for Fixed Dose Combination Products: Opportunities and Challenges”**, invited talk at the 2013 June LOL Conference on *Fixed Dose Combination Drug Development: Clinical, Formulation and Regulatory Challenges*, June 3-6, 2013, Madison, WI.
80. Panayiotis P. Constantinides **“Integrated Drug Discovery and Development Strategy and Models”**, invited talk and co-chair, *Session II R&D in Drug Innovation*, Bio Eco 2013, June 25-26, 2013, Tianjin Institute of Pharmaceutical Research, Tianjin, China.

81. Panayiotis P. Constantinides **“Nanoparticles Technologies in Drug Delivery : Design and Development Considerations and Case Studies”** invited seminar at Nankai University, College of Life Sciences, June 26, 2013, Tianjin, China.
82. Panayiotis P. Constantinides **“Trends and Perspectives in Oral Lipid-Based Formulations and Dosage Forms for Immediate, Sustained/Controlled Drug Release”**, invited seminar at CoSci Med-Tech Ltd, June 28, 2013, Beijing, China.
83. Panayiotis P. Constantinides **“Drug Emulsions/Microemulsions/Nanoemulsions : Quality Characteristics and Performance Assessment”**, invited talk in the mini-symposium *Overcoming Physical Stability Challenges with Multiphase Lipid Dispersed Systems and Impact on Product Quality and Performance*, 2013 AAPS Annual Meeting, November 10-14, 2013, San Antonio. TX.
84. Panayiotis P. Constantinides **“Enabling the Development and Life Cycle Management of Oral Poorly Soluble Drugs Using Lipid-Based Drug Delivery Systems”**, invited keynote talk at the *4th International Conference and Exhibition on Pharmaceuticals and Novel Drug Delivery Systems*, March 24-26, 2014 San Antonio, TX.
85. Panayiotis P. Constantinides **“Parenteral and Oral Nanoemulsions and Nanosuspensions: Processing, Characterization and In Vitro/In Vivo Performance Assessment”**, invited talk and Chair, *Solubility and Bioavailability Enhancement Workshop : Accelerating Translation of Challenging Compounds from Discovery to Clinical Testing and the Market*, Ascendia Pharmaceuticals, LLC, April 28, 2014, North Brunswick, NJ.
86. Panayiotis P. Constantinides **“Solubility and Bioavailability Enhancement in Drug Development : Drivers, Technologies to Consider and Assessment Strategies”**, invited keynote talk, Evonik's *5th Solubility and Bioavailability Enhancement Symposium Utilizing Pharmaceutical Melt Extrusion and Spray Drying Techniques*, May 13-14, 2014, South Plainfield, NJ.
87. Panayiotis P. Constantinides **“Advances in Parenteral Drug Nanodispersions : Processing, Characterization and Case Studies”**, invited talk at the *University of Nebraska Medical Center , Biopharma R&D Symposium*, June 5-6, 2014, Omaha, NE.
88. Panayiotis P. Constantinides **“Overview of Particle Engineering Needs in Pharma”**, co-organizer, speaker and panelist, Preconference Workshop on **“Particle Engineering Technology Selection and Partnership: A Roadmap to Commercialization”**, 2014 June LOL Conference, *“Particle Engineering in API and Drug Product Design”*, June 9-12, 2014, Madison, WI.
89. Panayiotis P. Constantinides **“Advancing Oral Peptide Formulations to Clinic and Commercialization : Development Considerations”**, invited talk at the Workshop *“Oral Peptide/Protein Delivery”*, July 12-13, 2014, CRS Annual Meeting, Chicago, Illinois.
90. Panayiotis P. Constantinides **“Oral Emulsions, Microemulsions and Reverse Micelles for BCS II/IV and III Molecules”**, invited talk at the *AAPS Workshop Improving Bioavailability by Lipid-Based Delivery Approaches*, November 1-2, 2014, San Diego, CA.
91. Panayiotis P. Constantinides **“Excipients as Inhibitors of the Absorption of Dietary Cholesterol : Principles and Case Studies with Nanostructured Aluminosilicates”**, invited

talk at the symposium on *Excipients as Atypical Actives in Nutraceuticals and Pharmaceuticals : Applications and Development Considerations*, 2014 AAPS Annual Meeting, November 2-6, 2014, San Diego, CA.

92. Panayiotis P. Constantinides **“Oral Lipid-Based Formulations as Enabling Strategy in Drug Discovery and Life Cycle Management”**, invited speaker and member of the organizing committee, *1st International Congress of Controlled Release Society-Greek Local Chapter*, May 27-28, 2015, Athens, GREECE.
93. Panayiotis P. Constantinides **“Non-Traditional Uses of Pharmaceutical Excipients : Applications and Development Considerations”**, invited speaker, *1st International Workshop of MD Pharmacon Pharmaceutical Services Ltd on Advances in Scientific-Regulatory Issues in Drug Development and Authorization Processes*, May 29, Athens, Greece.
94. Panayiotis P. Constantinides **“Parenteral Drug Nanodispersions : Manufacturing, Characterization and In Vitro/In Vivo Performance Evaluation”**, keynote talk at OMICS Parenterals-2015 Conference, August 17-19, 2015, Chicago, Illinois.
95. Panayiotis P. Constantinides **“Addressing Solubility and/or Permeability Challenges in Drug Development : Best Practices”**, speaker and organizer, short course on *Assessing and Applying Enabling Delivery Technologies and Formulation Tools to Oral Small Molecule (BSC II/IV) and Peptide Therapeutics (BCS III)*, 2015 AAPS Annual Meeting, October 25-29, Orlando, FL.
96. Panayiotis P. Constantinides **“Starting a New Pharma/Biotech Company or Consulting Business: Why, What and How?”** professional development mini-session, 2015 AAPS Annual Meeting, October 25-29, Orlando, FL.
97. Panayiotis P. Constantinides **“ Effective Use of Lipids in Drug Delivery : Key Considerations and Best Practices”** invited talk at the Workshop *Enabling the Development of Oral Therapeutics with Innovation in Lipid Formulation Technologies*, September 19-20, 2016, Plainsboro, NJ.
98. Panayiotis P. Constantinides **“Dispersed Systems for Oral Peptides Incorporating Permeation Enhancers and Peptide Stabilizers”** invited panelist in a dialogue and debate session *Getting Oral Peptides to the Market : To Conjugate and/or Disperse the Peptide?*, 2016 AAPS Annual Meeting, November 13-17, 2016, Denver, CO.
99. Panayiotis P. Constantinides **“Oral Lipid Formulation Case Studies: Linking Drug Product Quality to Performance”**, invited talk at the 2017 June Land O’Lakes Pharmaceutical Conference, *Material Sciences Approaches to Improving Drug Delivery Performance: From Discovery Through Manufacturing*, June 5-8, 2017, Madison, WI.
100. Panayiotis P. Constantinides **“Evolution of Excipient Use in Drug Products: Traditional and Non-traditional Uses and Implications in Excipient Selection and Formulation Development”**, invited talk AAPS Short Course *Pharmaceutical Excipients: Biopharmaceutical, Quality Control and Regulatory Considerations*, 2017 AAPS Annual Meeting, November 12-15, 2017, San Diego, CA.
101. Panayiotis P. Constantinides **“Academia-Industry Partnerships: Success Considerations and Lessons Learned”** invited talk in the symposium *Academia-Biotech/Pharma Industry*

Partnerships: Opportunities and Challenges, 2017 AAPS Annual Meeting, November 12-15, 2017, San Diego, CA.

102. Panayiotis P. Constantinides **“Development and Commercialization of Oral Peptides/Proteins: Trends and Perspectives”**, keynote talk at the *12th World Drug Delivery Summit*, September 24-26, 2018, Chicago, IL.
103. Panos P. Constantinides and Ronak Savla, co-presenters, **“Is an Oral Lipid-Based Formulation Best for Your Molecule? Insights from exclusive survey on strategies for poorly soluble molecules”**, March 27, 2019 Catalent Webinar.

Issued US and EP Patents

1. Laman A. Al-Razzak, Panayiotis P. Constantinides, Dilip Kaul, John Lipari, Lisa McChesney-Harris and Bashar Y. Abdullah **“Hydrophilic Binary Systems for the Administration of Lipophilic Compounds”**, *US Patent 6,008,192, December 28, 1999*. This invention discloses binary pharmaceutical compositions comprising (i) a cyclosporine compound, (ii) a hydrophilic phase and (iii) a surfactant, provide bioavailability of the active ingredient which is equivalent to that provided by ternary compositions, but without the need for a lipophilic phase.
2. Karel Lambert, Panayiotis P. Constantinides and Steven C. Quay **“Emulsion Vehicle for Poorly Soluble Drugs”**, *US 6,458,373, October 1, 2002*. An emulsion of α -tocopherol, stabilized by biocompatible surfactants, as a vehicle or carrier for therapeutic drugs, which is substantially ethanol-free and which can be administered to animals or humans by various routes is disclosed. Also included in the emulsion is PEGylated vitamin E. PEGylated α -tocopherol includes polyethylene glycol subunits attached by a succinic acid diester at the ring hydroxyl of vitamin E and serves as a primary surfactant, stabilizer and a secondary solvent in emulsions of α -tocopherol.
3. Panayiotis P. Constantinides, Karel Lambert, Alexander Tustian and Andrew Nienstedt, **“Compositions of Tocol-Soluble Therapeutics”**, *US 6,479,540, November 12, 2002*. Tocol-based compositions of charged amphiphilic and water soluble pharmaceutically active compounds or their charged precursors are prepared by forming a tocol-soluble ion pair with an oppositely charged ion-pair forming compound capable of forming a tocol-soluble ion-pair with the active compound. Also disclosed are novel compounds tocopherolsuccinate-aspartate and tocopherolsuccinate-glutamate, which are useful as ion-pair forming compounds.
4. Karel Lambert, Panayiotis P. Constantinides, Alex Tustian and Steven C. Quay, **“Emulsion Vehicle for Poorly Soluble Drugs”**, *US 6,660,286, December 9, 2003*. An emulsion incorporating one or more tocopherols, a co-solvent and, stabilized by biocompatible surfactants, as a vehicle or carrier for therapeutic drugs, which is substantially ethanol free and which can be administered to animals or humans by various routes is disclosed. Also included in the emulsion is PEGylated vitamin E, PEGylated α -tocopherol includes polyethylene glycol subunits attached by a succinic acid diester at the ring hydroxyl of vitamin E and serves as a primary surfactant, stabilizer and a secondary solvent in tocol emulsions.
5. Karel Lambert, Panayiotis P. Constantinides, Alex Tustian and Steven C. Quay, **“Emulsion Vehicle for Poorly Soluble Drugs”**, *US 6,667,048, December 12, 2003*.
6. Robert E. Dudley and Panayiotis P. Constantinides, **“Pharmaceutical Delivery Systems for Hydrophobic Drugs and Compositions Comprising Same”**, *US 8,241,664, August 14, 2012*.

7. Robert E. Dudley and Panayiotis P. Constantinides, **“Pharmaceutical Delivery Systems for Hydrophobic Drugs and Compositions Comprising Same”**, EP1871384, 1/2/2008.
8. Panayiotis P. Constantinides, Likan Liang and Eun-Hyun Jang, **“Stabilized Reverse Micelle Compositions and Uses Thereof”**, EP 1460992, 3/11/2009.
9. Panayiotis P. Constantinides, Likan Liang and Eun-Hyun Jang, **“Stabilized Reverse Micelle Compositions and Uses Thereof”**, US 8,535,650, September 17, 2013.
10. Arthur Michaelis and Panayiotis P. Constantinides, **“Pharmaceutical Compositions and Uses Thereof”**, EP2056835, 5/13/2009.
11. Jerald W. Darlington and Panayiotis P. Constantinides, **“Cholesterol-Interacting Layered Phyllosilicates and Methods of Reducing Hypercholesteremia in a Mammal”**, EP2167069, 10/26/2011. Layered phyllosilicates are useful for adsorbing and/or binding to cholesterol and, thereby, reducing blood cholesterol in a patient. Accordingly, provided herein is a method of reducing hypercholesteremia in a mammal comprising administering to said mammal a layered phyllosilicate material alone and in combination with other cholesterol-reducing agents in an amount effective to reduce hypercholesteremia in said mammal.
12. Jerald W. Darlington and Panayiotis P. Constantinides, **“Cholesterol-Interacting Layered Phyllosilicates and Methods of Reducing Hypercholesteremia in a Mammal”**, US 8,481,084, July 9, 2013.
13. Robert E. Dudley and Panayiotis P. Constantinides, **“Oral Testosterone Ester Formulations and Methods of Treating Testosterone Deficiency Comprising Same”**, US 8,492,369, July 23, 2013.
14. Robert E. Dudley and Panayiotis P. Constantinides, **“Oral Testosterone Ester Formulations and Methods of Treating Testosterone Deficiency Comprising Same”**, US 8,778,916, July 15, 2014.
15. Robert E. Dudley and Panayiotis P. Constantinides, **“Pharmaceutical Delivery Systems for Hydrophobic Drugs and Compositions Comprising Same”**, US 8,778,917, July 15, 2014.
16. Robert E. Dudley and Panayiotis P. Constantinides, **“Pharmaceutical Delivery Systems for Hydrophobic Drugs and Compositions Comprising Same”**, US 8,828,428, September 9, 2014.
17. Wael Salameh and Panayiotis P. Constantinides **“Use of Oral Pharmaceutical Products Combining Testosterone Esters with Hypolipidemic Agents”**, US 10,245,273, April 2, 2019.
18. Robert E. Dudley and Panayiotis P. Constantinides, **“Pharmaceutical Delivery Systems for Hydrophobic Drugs and Compositions Comprising Same”**, US 11,179, 402, November 23, 2021.
19. Robert E. Dudley and Panayiotis P. Constantinides, **“Oral Testosterone Ester Formulations and Methods of Treating Testosterone Deficiency Comprising Same”**, US 11, 179, 403, November 23, 2021.
20. Christopher Kevil, Anthony Giordano, Douglas R. Flanagan and Panayiotis P. Constantinides **“Pharmaceutical Formulations of Nitrite and Uses Thereof”**, US 10,307,441, June 4, 2019.

21. Christopher Kevil, Anthony Giordano, Douglas R. Flanagan and Panayiotis P. Constantinides **"Pharmaceutical Formulations of Nitrite and Uses Thereof"**, US 10,463,689, November 5, 2019.

WO Patents

- A. The following patents disclose **"Microemulsion Compositions with Improved Drug Delivery/Absorption Characteristics"** Drug Delivery Department, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania.
 1. Panayiotis P. Constantinides, **"W/O Microemulsions"**, **WO 93/02664, 18 February 1993**, describes water-in-oil microemulsion compositions where the lipophilic phase is comprising of medium-chain glycerides (mono-, di-, and triglycerides).
 2. Panayiotis P. Constantinides, **"W/O Microemulsions"**, **WO 93/02665, 18 February 1993**, describes water-in-oil microemulsion compositions where the lipophilic phase is comprising of long-chain glycerides and sorbitan esters.
 3. Panayiotis P. Constantinides, **"Compositions"**, **WO 94 / 08603, 28 April 1994**, describes water-in-oil microemulsions where the lipophilic phase is comprising interesterified medium- and long-chain glycerides or sorbitan esters.
 4. Panayiotis P. Constantinides, **"Therapeutic Microemulsions"**, **WO 94 / 08605, 28 April 1994**, describes microemulsion compositions where the lipophilic phase is comprising physical mixtures of medium- and long-chain glycerides or sorbitan esters.
 5. Panayiotis P. Constantinides and Seang H. Yiv, **"Pharmaceutical Emulsion Compositions"** **WO 94 / 08610, 28 April 1994**, describes microemulsion compositions where the lipophilic phase is comprising in addition to glycerides (mono-, di-, triglycerides) or sorbitan esters, medium-chain fatty acids/salts.
 6. Panayiotis P. Constantinides, **"Microemulsions Containing Pharmaceutical Compositions"**, **WO 94/19000, 1 September, 1994**, describes pharmaceutical compositions in the form of microemulsions comprising an oil, a mixture of high and low HLB surfactants in which the high HLB surfactant comprises an aliphatic, aryl or aliphatic-aryl sulfate, sulfonate or sulfosuccinate or salt thereof, an aqueous phase and a biologically active agent.
 7. Panayiotis P. Constantinides, **"Microemulsions Comprising Therapeutic Peptides"**, **WO 94/19001, 1 September, 1994**, describes pharmaceutical compositions in the form of microemulsions comprising an oil, a mixture of high and low HLB surfactants in which the high HLB surfactant comprises a medium-chain alkyl/dialkyl sulfate, sulfonate or sulfosuccinate salt dissolved in a polyhydric alcohol, an aqueous phase and optionally further comprises a biologically active agent.
 8. Panayiotis P. Constantinides, **"Pharmaceutical Compositions"**, **WO94/19003, 1 September, 1994**, describes pharmaceutical compositions in the form of microemulsions comprising an oil, a mixture of high and low HLB surfactants in which the oil is a propylene glycol or polyol ester of medium-chain fatty acids, and high HLB surfactant comprises a medium-chain alkyl/dialkyl sulfate, sulfonate or sulfosuccinate salt dissolved in a polyhydric alcohol, an aqueous phase and optionally further comprises a biologically active agent.

9. Panayiotis P. Constantinides, "**Camptothecin Formulations**", WO 95/08986, 6 April 1995. This invention provides for the novel formulations of Camptothecin and its structurally related analogs in multilamellar or unilamellar vesicles. These novel formulations provide improved pharmacokinetics and pharmacodynamics for the compounds herein and thereby lowering the dose-dependent toxicity for use in anticancer treatments.
- B. The following discloses "**Self-emulsifying lipid-based systems for oral administration of lipophilic drugs**", Formulation Development Center, Pharmaceutical & Analytical R&D, Pharmaceutical Products Division, Abbott Laboratories, North Chicago, Illinois.
 1. Laman A. Al-Razzak, Panayiotis P. Constantinides, Rong Gao, Dilip Kaul, John Lipari, Terrence Mazer and Lisa McChesney-Harris "**Lipophilic Binary Systems for the Administration of Lipophilic Compounds**", WO98/40051, 17 September 1998. This invention discloses binary pharmaceutical formulations comprising (i) a cyclosporine compound, (ii) a lipophilic phase and (iii) a surfactant provide bioavailability of the active ingredient which is equivalent to that provided by ternary compositions, but without the need for a hydrophilic phase.
- C. The following patents disclose were filed by SONUS Pharmaceuticals, Bothell, Washington.
 1. Karel Lambert, Dean Kessler, Andrew Nienstedt, Greg Hartgraves and Panayiotis P. Constantinides "**Tocol-Based Compositions Containing Amiodarone**", AU 9482601, 8 April 2002.
 2. Nagesh Palepu, Dean Kessler, Alexander K. Tustian, Steven C. Quay, Panayiotis P. Constantinides and Karel J. Lambert, "**Method for Treating Colorectal Carcinoma Using a Taxane/Tocopherol Formulation**", US2003087954, 8 May, 2003.
- D. The following patent applications filed with the US PTO by DOR BioPharma, disclose **Lipid Polymer Micelles (LPM™)** for the delivery of water-soluble drugs/peptides (1, 2) and **Lipid Polymer Emulsions (LPE™)** and **Polymer Lipid Particles (PLP™)** for the solubilization and delivery of water-insoluble drugs (3,4):
 1. Eun-Hyun, Likan Liang and Panayiotis P. Constantinides, "**Reverse Micelle Compositions and Uses Thereof**", WO 03047494, 12 June, 2003.
 2. Eun-Hyun, Likan Liang and Panayiotis P. Constantinides, "**Stabilized Reverse Micelle Compositions and Uses Thereof**", WO 03047493, 12 June, 2003.
 3. Panayiotis P. Constantinides, Likan Liang and Reena Patil, "**Lipid Particles and Suspensions and Uses Thereof**", WO 03057128, 17 July, 2003.
 4. Panayiotis P. Constantinides, Likan Liang, Reena Patil and Elijah Bolotin, "**Monoterpene Compositions and Uses Thereof**", WO 03057193, 17 July, 2003
- E. Co-inventor in the following published patent applications with client companies.
 22. Robert E. Dudley and Panayiotis P. Constantinides, "**Pharmaceutical Delivery Systems for Hydrophobic Drugs and Compositions Comprising Same**", WO 113505A2, 26 October 2006. A drug delivery system for oral administration of hydrophobic drugs with enhanced and extended absorption and improved pharmacokinetics is provided. In one embodiment, formulation comprising testosterone and testosterone esters, e.g. testosterone palmitate, are disclosed. Methods of treating a hormone deficiency or effective male contraception with the inventive formulations are also provided.

23. Arthur Michaelis and Panayiotis P. Constantinides, **“Pharmaceutical Compositions and Uses Thereof”**, WO 117556A2, 18 October 2007. It features pharmaceutical compositions including Rifalazil, a surfactant, and a lipophilic antioxidant and methods of use thereof.
24. John Hughes, Jerald W. Darlington, Jr., and Panayiotis P. Constantinides, **“Virus-Interacting Layered Phyllosilicates and Methods of Inactivating Viruses on Animate and Inanimate Surfaces”**, US 2007/ 0224293 A1, 27 September, 2007. Layered phyllosilicates are useful for adsorbing and/or binding to and, thereby, inactivating viruses. Accordingly, provided herein is a method of inhibiting transfer of a virus to a surface comprising contacting the surface with a composition comprising a layered phyllosilicate material in an amount sufficient for inhibiting the transfer of the virus thereto. Also provided are methods of inactivating a virus on a surface comprising contacting the surface with a composition comprising a layered phyllosilicate material in an amount sufficient to inactivate said virus.
25. John Hughes, Panayiotis P. Constantinides, and Jerald W. Darlington, Jr. **“Virus-Interacting Layered Phyllosilicates and Methods of Inactivating Viruses in the Gastrointestinal Tract”**, US 2007/ 0231412 A1, 4 October, 2007. Layered phyllosilicates are useful for adsorbing and/or binding to and, thereby, inactivating viruses. Accordingly, provided herein is a method of inactivating a virus in the gastrointestinal tract of a mammalian subject comprising administering to said subject a composition comprising a layered phyllosilicate material in an amount effective for virus inactivation. Also provided are methods of treating a viral infection in the gastrointestinal tract of a mammalian subject. Methods of delivering a therapeutic agent to a mammalian subject and methods of inactivating a virus in waste expelled from a mammal are also provided.
26. Christopher Kevil, Anthony Giordano, Douglas R. Flanagan and Panayiotis P. Constantinides **“Pharmaceutical Formulations of Nitrite and Uses Thereof”**, US2011/0086069 A1, April 14, 2011. The present invention relates to pharmaceutical compositions of nitrites such as inorganic nitrites, or any pharmaceutically acceptable salts, solvates, or prodrugs thereof, and the medical use of these compositions. The pharmaceutical compositions, which can be formulated for oral administration, can provide immediate release or extended release of the nitrite ion (NO_2^-). The pharmaceutical compositions of the invention are useful, for example, for the treatment of chronic ischemia.
27. Christopher Kevil, Anthony Giordano, Douglas R. Flanagan and Panayiotis P. Constantinides **“Pharmaceutical Formulations of Nitrite and Uses Thereof”**, EP10824097, 31 July 2013.
28. Wael Salameh and Panayiotis P. Constantinides **“Use of Oral Pharmaceutical Products Combining Testosterone Esters with Hypolipidemic Agents”**, WO 2015/100406.
29. Robert E. Dudley, Panayiotis P. Constantinides and James A. Longstreth **“Methods of Treating Testosterone Deficiency”**, US 2017/0246184, August 31, 2017.

Panayiotis P. Constantinides, Ph.D. Expert Testimony 2015 - Present

In 2015, I have testified as an expert witness in the following arbitrations and litigations:

- *Alnylam v Tekmira, Case No-50 122T 0072613, ICDR, New York* (arbitration panel).

From 2018 – present, I have also testified in Depositions in the following litigation cases, the first three on patent litigations and the last one on a breach of contract litigation:

- *Collegium Pharmaceuticals Inc. v Purdue Pharmaceuticals, L.P., et al., Case No. PGR2018-00048, United States Patent Trial and Appeal Board*
- *Purdue Pharma L.P., et al. v. Collegium Pharmaceutical Inc., C.A. No. 1:15-cv-13099-FDS, U.S.D.C. (D.Mass)*
- *Almirall v. Taro Pharmaceutical Industries Ltd., et al., C.A. No. 1:17-cv-00663-JFB, U.S.D.C. (D.Del.)*
- *Intervet Inc. v Mileuits Ltd., C.A. No. 3:15-cv-01371-FLW, U.S.D.C. (D.NJ)*

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPANED safely and effectively. See full prescribing information for EPANED.

EPANED® (enalapril) for Oral Solution
Initial U.S. Approval: 1985

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- When pregnancy is detected, discontinue EPANED as soon as possible. (5.1)
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)

RECENT MAJOR CHANGES

Indications and Usage (1) 09/2014
Dosage and Administration (2) 09/2014

INDICATIONS AND USAGE

EPANED is an angiotensin-converting enzyme inhibitor indicated for:

- treatment of hypertension in adults and children older than one month, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1.1)
- treatment of symptomatic heart failure. (1.2)
- treatment of asymptomatic left ventricular dysfunction, to decrease the rate of development of overt heart failure and reduce hospitalization for heart failure (1.3)

DOSAGE AND ADMINISTRATION

Hypertension

- Adult: recommended initial dose is 5 mg once daily. Maximum dose is 40 mg daily. (2.1)
- Pediatrics: recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. (2.1)
- Heart Failure: Initiate at 2.5 mg twice daily. Titrate up to 20 mg twice daily as tolerated (2.2)

Asymptomatic Left Ventricular Dysfunction: Initiate at 2.5 mg twice daily. Titrate up to 10 mg twice daily. (2.3)

FULL PRESCRIBING INFORMATION: CONTENTS***WARNING: FETAL TOXICITY****1 INDICATIONS AND USAGE**

- Hypertension
- Heart Failure
- Asymptomatic Left Ventricular Dysfunction

2 DOSAGE AND ADMINISTRATION

- Hypertension
- Heart Failure
- Asymptomatic Left Ventricular Dysfunction
- Preparation of EPANED (for 150 mL, 1 mg/mL enalapril solution)

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- Fetal Toxicity
- Angioedema and Anaphylactoid Reactions
- Hypotension
- Hepatic Failure
- Impaired Renal Function
- Hyperkalemia

6 ADVERSE REACTIONS

- Clinical Trials Experience
- Other Adverse Reactions from Clinical Studies or Postmarketing Experience

DOSAGE FORMS AND STRENGTHS

EPANED Powder for Oral Solution contains 150 mg of enalapril maleate in a 150 mL bottle. Reconstitution with 150 mL of ORA-SWEET® SF provided results in a 1 mg/mL EPANED oral solution. (3)

CONTRAINDICATIONS

- Hypersensitivity related to previous treatment with an ACEI. (4)
- Hereditary or idiopathic angioedema. (4)
- Do not co-administer aliskiren in patients with diabetes. (4)

WARNINGS AND PRECAUTIONS

- Angioedema and Anaphylactoid Reactions. (5.2)
- Impaired Renal Function: Assess renal function. (5.5)
- Hyperkalemia. (5.6)

ADVERSE REACTIONS

- The most common adverse reaction for patients treated for hypertension ($\geq 3\%$) was fatigue (6.1).
- The most common adverse reactions for patients treated for heart failure ($> 6\%$) were hypotension and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Silvergate Pharmaceuticals at 1-855-379-0383 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- In patients who are elderly, volume-depleted (as on diuretic therapy), or with compromised renal function, use with NSAIDs, including selective COX-2 inhibitors, may result in deterioration of renal function, including renal failure. Monitor renal function periodically. (7.1)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension and hyperkalemia. (7.2)
- Avoid potassium sparing agents in patients with heart failure. (7.3)
- Monitor serum lithium levels frequently. (7.4)

USE IN SPECIFIC POPULATIONS

- EPANED is not recommended in neonates and in pediatric patients with glomerular filtration rate < 30 mL/min/1.73m². (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2014

7 DRUG INTERACTIONS

- Non-Steroidal Anti-Inflammatory Agents (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)
- Dual Blockade of the Renin-Angiotensin System (RAS)
- Agents Increasing Serum Potassium
- Lithium
- Gold

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Nursing Mothers
- Pediatric Use

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- Heart Failure, Mortality Trials

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed

DTX-1073

Reference ID: 3621988

Appx2208

Exhibit #

Little 04

06/14/22 - AS

exhibitsticker.com

Limited data are available in regard to overdosage in humans.

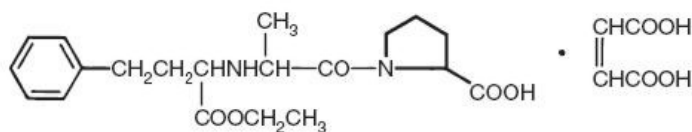
Single oral doses of enalapril above 1,000 mg/kg and $\geq 1,775$ mg/kg were associated with lethality in mice and rats, respectively.

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Enalaprilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis.

11 DESCRIPTION

EPANED (Enalapril Maleate) Powder for Oral Solution is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin-converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, and its structural formula is:



Enalapril maleate is a white to off-white, crystalline powder with a molecular weight of 492.52. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin-converting enzyme inhibitor.

EPANED Powder for Oral Solution is a kit consisting of 1 bottle containing a dry powder blend of enalapril maleate, USP, mannitol, and colloidal silicon dioxide and 1 bottle of Ora-Sweet SF diluent for reconstitution resulting in a 1 mg/mL EPANED oral solution. The Ora-Sweet SF diluent contains: purified water, glycerin, sorbitol, sodium saccharin, xanthan gum, and flavoring. Buffered with citric acid and sodium citrate. Preserved with methylparaben (0.03%), propylparaben (0.008%), and potassium sorbate (0.1%).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased

- **Angioedema**

Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin-converting enzyme inhibitors, including enalapril. Advise patients to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, or tongue, or difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

- **Hypotension**

Caution patients to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, tell patients to discontinue the drug until they have consulted with the prescribing physician.

Tell patients that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; advise patients to consult with their physician.

- **Hyperkalemia**

Tell patients not to use salt substitutes containing potassium without consulting their physician.

EPANED is a registered trademark of Silvergate Pharmaceuticals, Inc.
Ora-Sweet SF is a registered trademark of Paddock Laboratories, Inc.
VASOTEC is a registered trademark of Valeant International Bermuda.

Manufactured For:
Silvergate Pharmaceuticals, Inc.
6251 Greenwood Plaza Blvd., Suite 101
Greenwood Village, CO 80111

U. S. Patents 8568747; 8778366

EN-1408

Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids

Exhibit #**Little 05**

06/14/22 - AS

LOYD V. ALLEN, JR., AND MARTIN A. ERICKSON III

Abstract: The stability of five drugs commonly prescribed for use in oral liquid dosage forms but not commercially available as such was studied.

Alprazolam 1 mg/mL, chloroquine phosphate 15 mg/mL, cisapride 1 mg/mL, enalapril maleate 1 mg/mL, and hydralazine hydrochloride 4 mg/mL were each prepared in a 1:1 mixture of Ora-Sweet and Ora-Plus (Paddock Laboratories), a 1:1 mixture of Ora-Sweet SF and Ora-Plus, and cherry syrup and placed in 120-mL amber clear polyethylene terephthalate bottles. Three bottles of each liquid

were stored at 5 °C and three at 25 °C, all in the dark. Samples were taken initially and at various times up to 60 days for analysis by high-performance liquid chromatography and assessment of appearance and odor; pH was measured.

A mean of at least 91% of the initial drug concentration was retained for 60 days in the alprazolam, chloroquine phosphate, cisapride, and enalapril maleate liquids. The hydralazine hydrochloride liquids retained more than 90% of the initial concentration for only one day at 5 °C when prepared with Ora-

Sweet–Ora-Plus and two days when prepared with Ora-Sweet SF–Ora-Plus and for less than a day in these preparations at 25 °C and in cherry syrup at 5 and 25 °C. No substantial changes in the appearance, odor, or pH of any liquid were observed.

Alprazolam 1 mg/mL, chloroquine phosphate 15 mg/mL, cisapride 1 mg/mL, and enalapril maleate 1 mg/mL were stable in three extemporaneously compounded oral liquids for 60 days at 5 and 25 °C; hydralazine hydrochloride 4 mg/mL was stable at 5 °C for one day in Ora-Sweet–Ora Plus and for two days in

Ora-Sweet SF–Ora-Plus.

Index terms: Alprazolam; Antimalarial agents; Anxiolytics, sedatives and hypnotics; Cherry syrup; Chloroquine phosphate; Cisapride; Compounding; Containers; Enalapril maleate; Gastrointestinal drugs; Hydralazine hydrochloride; Hypotensive agents; Incompatibilities; Liquids; Polyethylene terephthalate; Stability; Storage; Sweetening agents; Syrups; Temperature; Vehicles

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This article is the sixth in a series on the stability of drugs in extemporaneously prepared oral liquids.¹⁻⁵

Methods

Alprazolam^a 1 mg/mL, chloroquine phosphate^b 15 mg/mL, cisapride^c 1 mg/mL, enalapril maleate^d 1 mg/mL, and hydralazine hydrochloride^e 4 mg/mL were prepared in a 1:1 mixture of Ora-Sweet^f and Ora-Plus,^g a 1:1 mixture of Ora-Sweet SF^h and Ora-Plus, and cherry syrup (cherry syrup concentrateⁱ diluted 1:4 with simple syrup, according to label directions). Each liquid was stored in the dark for 60 days at 5 and 25 °C in 120-mL amber clear polyethylene terephthalate prescription ovals with low-density polyethylene foam cap linings.^j The source of the drugs was commercially available tablets. Details of the compounding proce-

dures are given in the appendix.

The experimental method was identical to that previously reported.¹ The samples were analyzed by using stability-indicating high-performance liquid chromatographic assays from the literature⁶⁻⁸ or USP monographs^{9,10} (Table 1 and Figures 1–5). The assay for cisapride was modified by using a C₁₈ column in place of a C₈ column and by using a solution of 0.05 M ammonium acetate in place of water and diethylamine in place of triethylamine for the mobile phase, as well as replacing a portion of the acetonitrile with methanol.

Stability was defined as the retention of not less than 90% of the original drug concentration.

Results

Visual and olfactory observations did not reveal any substantial changes during the study period.

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Table 1.
High-Performance Chromatographic Conditions

Drug (Dilution)	Column	Mobile Phase	Flow Rate (mL/min)	Detector Setting (nm)	Retention Time (min)	Range of Standard Curve (μg/mL)	Coefficient of Variation (%)	
							Intraday	Interday
Alprazolam ⁶ (1:50)	C ₁₈ ^a	Methanol:acetonitrile:0.04 M sodium acetate in water (pH 2.4) (45:8:47)	0.6	230	9.9	1–25 ^b	1.4	2.3
Chloroquine phosphate ⁷ (1:100)	C ₁₈	0.02 M 1-heptanesulfonic acid (pH 3.4):acetonitrile (66:34)	1.5	340	9.4	10–150 ^c	0.8	1.9
Cisapride ⁸ (1:50) (modified assay)	C ₁₈	0.05 ammonium acetate in water:acetonitrile: methanol (1:1:1) adjusted to pH 8 with diethylamine	1.0	276	7.5	1–25 ^d	1.1	1.6
Enalapril maleate ⁹ (1:10)	C ₈ ^e	Water:acetonitrile: buffer solution (136 g of monobasic potassium phosphate in 800 mL of water, with pH adjusted to 4.0, diluted to 1000 mL with water) (34:15:1)	1.5	215	8.8	10–100 ^f	2.1	2.4
Hydralazine hydrochloride ¹⁰ (1:50)	Cyano ^g	1.44 g of dodecyl sodium sulfate, 0.75 g of tetrabutyl-ammonium bromide in 770 mL of water and 230 mL of acetonitrile, with pH adjusted to 3.0 with 0.1 N sulfuric acid	1.0	230	7.5	10–100 ^h	2.3	3.0

^aBakerbond C₁₈ column, 5 μm, 4.6 x 250 mm, J. T. Baker, Inc., Phillipsburg, NJ.
^bAlprazolam reference standard, United States Pharmacopeia, Rockville, MD, lot G.
^cChloroquine phosphate reference standard, United States Pharmacopeia, lot H.
^dCisapride reference standard, Janssen Research Foundation, Belgium, lot PUA-192.
^eBakerbond C₈ column, 5 μm, 4.6 x 250 mm, J. T. Baker.
^fEnalapril maleate reference standard, United States Pharmacopeia, lot H.
^gBakerbond cyano column, 5 μm, 4.6 x 250 mm, J.T. Baker.
^hHydralazine hydrochloride reference standard, United States Pharmacopeia, lot J.

Figure 1. Chromatograms of intact (A) and degraded (B, a composite) alprazolam.

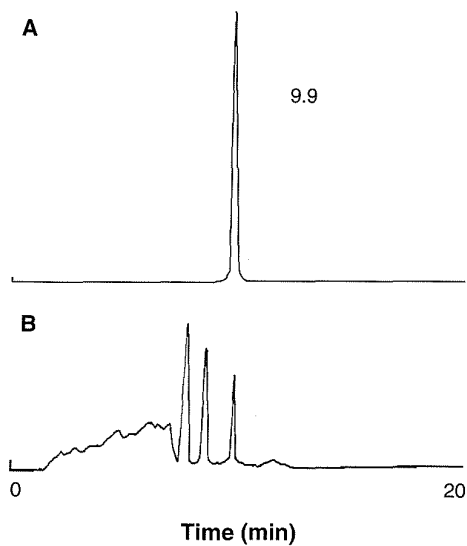


Figure 2. Chromatograms of intact (A) and degraded (B, a composite) chloroquine phosphate.

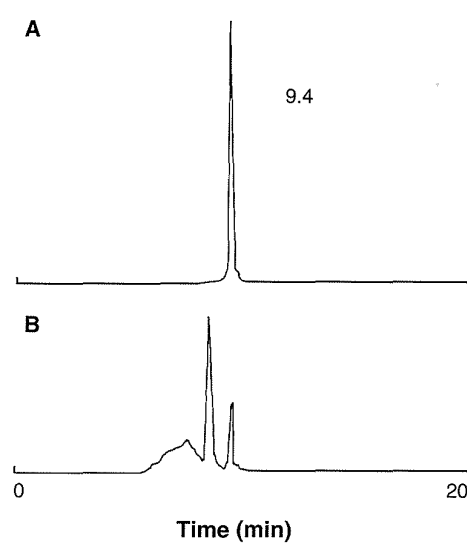
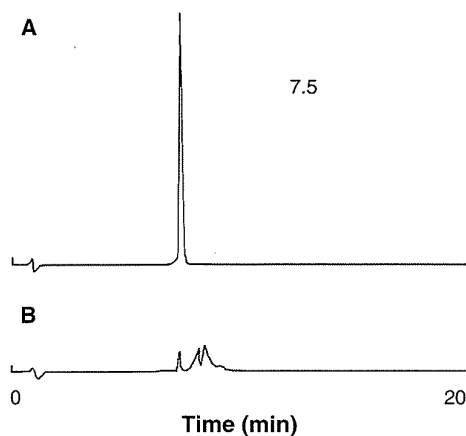
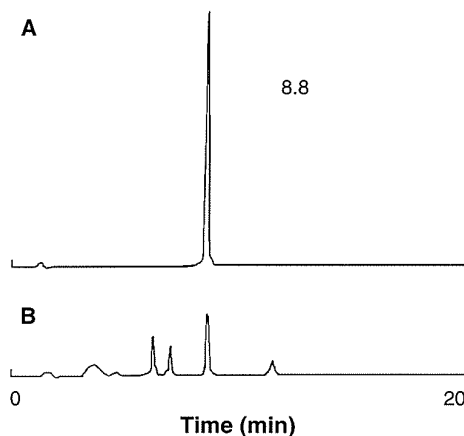
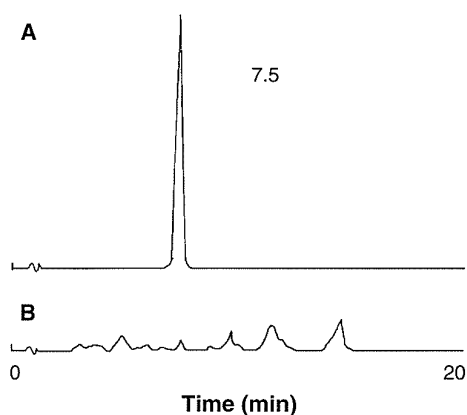


Figure 3. Chromatograms of intact (A) and degraded (B, a composite) cisapride.**Figure 4.** Chromatograms of intact (A) and degraded (B, a composite) enalapril maleate.**Figure 5.** Chromatograms of intact (A) and degraded (B, a composite) hydralazine hydrochloride.

For the oral liquids prepared with Ora-Sweet–Ora-Plus or Ora-Sweet SF–Ora-Plus, the initial apparent pH values were as follows: alprazolam, 4.5–4.7; chloroquine phosphate, 4.5; cisapride, 7.0; enalapril maleate, 4.7–4.8; and hydralazine hydrochloride, 4.3–4.4. For the oral liquids prepared with cherry syrup, the initial apparent pH values were as follows: alprazolam, 3.8; chloroquine phosphate, 3.8; cisapride, 7.1; enalapril maleate, 3.9; and hydralazine hydrochloride, 3.8. Throughout the study, the change in the apparent pH values of the oral liquids was <0.5 pH unit.

Except for the oral liquids containing hydralazine hydrochloride, a mean of at least 91% of the initial drug concentration remained in all liquids for up to 60 days (Table 2).

Discussion

Alprazolam is a white to off-white, crystalline powder that is insoluble in water and soluble in alcohol.¹¹ The stability of alprazolam in vehicles such as those used in this study may be partly attributed to the drug's poor aqueous solubility.

The results for the chloroquine phosphate 15-mg/mL oral liquids agree with those of Odusote and Nasipuri,¹² who reported on the stability of chloroquine phosphate in three formulations over 12 weeks. The vehicles used were either sucrose syrups or methylcellulose solutions (with pH adjusted to 4.5–4.9) containing preservatives, coloring, and other excipients. Another study found chloroquine phosphate to be stable for at least 30 days in a 25-mg/mL suspension at a pH of 4–6.¹³ An additional study showed chloroquine phosphate 20 mg/mL in simple syrup to be physically stable after storage at 49 °C for 63 hours and after storage at –6 °C for 8 hours before being returned to room temperature.¹⁴ The drug is a white, odorless, crystalline powder with a bitter taste and exists in two polymorphic forms. It is freely soluble in water,¹⁵ so the chloroquine phosphate preparations used in this study were solutions of the drug.

Cisapride 1 mg/mL was shown by Nahata et al.⁸ to be stable for at least 91 days in a vehicle of 1% methylcellulose and simple syrup when refrigerated and for 28 days when stored at room temperature. In a study by Horn and Anderson,¹⁶ the drug was stable in a formulation consisting of cherry syrup and propylene glycol, with the pH adjusted to >6.5, at room temperature for at least three weeks. To improve the drug's stability in a liquid, it is important to adjust the pH to neutral (if it is not already), as we did.

Enalapril maleate is a white to off-white, crystalline powder that is soluble in water to a concentration of 25 mg/mL and in alcohol to a concentration of 80 mg/mL.¹⁷ It has pK_a values of 3 and 5.4 and is reported to have maximum stability at a pH of ~3.¹⁸ At a pH >5, the rate of decomposition increases. One study, conducted at room temperature, found that 0.5-mg/mL enalapril maleate solutions at pH 2 and 5 were stable for 262 and

Table 2.
Stability of Alprazolam 1 mg/mL, Chloroquine Phosphate 15 mg/mL, Cisapride 1 mg/mL, Enalapril Maleate 1 mg/mL, and Hydralazine Hydrochloride 4 mg/mL in Sweetened Vehicles at 5 and 25 °C

Drug and Storage Time (Days)	% Initial Concentration Remaining ^a					
	1:1 Mixture of Ora-Sweet and Ora-Plus		1:1 Mixture of Ora-Sweet SF and Ora-Plus		Cherry Syrup	
	5 °C	25 °C	5 °C	25 °C	5 °C	25 °C
Alprazolam ^b						
1	99.3 ± 0.9	99.0 ± 0.7	99.7 ± 0.8	99.9 ± 0.4	99.8 ± 0.6	99.8 ± 0.8
2	99.5 ± 1.1	95.9 ± 0.7	99.5 ± 0.3	99.5 ± 0.9	99.2 ± 0.4	99.5 ± 0.9
7	99.2 ± 0.6	94.7 ± 0.9	99.4 ± 1.1	99.2 ± 1.1	99.1 ± 1.1	98.6 ± 0.8
10	99.7 ± 1.3	95.2 ± 1.1	99.2 ± 0.9	98.6 ± 1.3	99.2 ± 1.0	98.7 ± 0.7
14	99.0 ± 0.8	93.9 ± 1.2	98.9 ± 1.0	98.8 ± 0.7	97.0 ± 0.9	96.9 ± 1.1
28	97.8 ± 1.1	93.6 ± 0.9	98.6 ± 0.5	98.2 ± 0.9	96.6 ± 1.2	95.4 ± 0.9
35	98.1 ± 0.9	95.2 ± 0.8	97.4 ± 0.7	97.9 ± 0.5	95.8 ± 1.1	93.3 ± 0.8
60	96.6 ± 0.7	95.4 ± 0.6	97.7 ± 0.9	96.4 ± 1.1	93.9 ± 0.9	91.4 ± 0.5
Chloroquine phosphate ^c						
1	99.5 ± 0.5	99.9 ± 1.1	99.5 ± 0.9	99.8 ± 1.3	100.0 ± 0.8	98.9 ± 1.2
2	99.5 ± 0.7	99.6 ± 0.9	99.5 ± 0.4	99.8 ± 0.8	100.2 ± 0.8	100.1 ± 1.0
7	98.5 ± 0.9	98.8 ± 1.3	99.6 ± 0.5	98.7 ± 1.2	99.3 ± 0.4	99.5 ± 0.9
10	99.2 ± 1.2	99.2 ± 0.9	99.4 ± 1.1	98.9 ± 0.9	98.8 ± 1.0	99.1 ± 1.0
14	99.1 ± 1.1	99.5 ± 0.8	99.5 ± 0.2	99.0 ± 0.6	99.4 ± 0.9	98.6 ± 0.7
28	97.9 ± 0.8	99.3 ± 1.1	99.2 ± 1.0	98.8 ± 1.1	98.7 ± 1.2	99.5 ± 0.9
35	98.4 ± 0.7	98.7 ± 1.0	99.1 ± 1.4	98.9 ± 1.2	99.0 ± 1.1	98.9 ± 0.8
60	98.1 ± 0.5	99.0 ± 0.6	99.3 ± 0.8	98.8 ± 0.9	99.4 ± 0.7	99.3 ± 0.6
Cisapride ^d						
1	99.5 ± 0.7	99.8 ± 0.9	99.2 ± 1.1	99.0 ± 1.5	98.4 ± 1.0	99.5 ± 0.9
2	100.1 ± 1.1	100.2 ± 1.0	99.1 ± 1.0	98.6 ± 1.2	99.1 ± 1.1	98.7 ± 0.8
7	100.6 ± 0.9	99.6 ± 0.9	98.5 ± 1.4	97.1 ± 0.9	97.5 ± 0.2	99.3 ± 0.9
10	100.5 ± 0.9	98.5 ± 1.4	97.9 ± 0.3	96.3 ± 1.2	96.5 ± 0.4	97.4 ± 1.3
14	98.2 ± 0.4	97.4 ± 0.9	96.3 ± 0.9	95.7 ± 1.1	96.1 ± 0.9	93.1 ± 1.4
28	99.6 ± 1.2	96.8 ± 1.0	95.9 ± 0.8	94.9 ± 0.7	93.8 ± 0.7	94.7 ± 0.9
35	97.7 ± 1.1	93.9 ± 1.2	95.7 ± 0.9	94.5 ± 0.9	94.9 ± 0.8	92.8 ± 0.9
60	97.9 ± 0.8	93.8 ± 1.1	94.2 ± 0.7	92.9 ± 0.8	92.9 ± 0.8	91.0 ± 0.4
Enalapril maleate ^e						
1	98.7 ± 1.5	99.5 ± 1.1	99.9 ± 1.5	99.8 ± 1.2	97.2 ± 1.0	99.7 ± 0.9
2	98.6 ± 1.4	100.4 ± 0.9	99.7 ± 1.3	99.6 ± 0.7	97.1 ± 0.7	99.7 ± 1.3
7	98.3 ± 0.9	100.8 ± 1.1	99.8 ± 0.8	99.7 ± 0.9	97.0 ± 0.6	99.5 ± 0.9
10	97.9 ± 1.0	99.3 ± 1.3	98.6 ± 0.4	98.9 ± 0.8	98.4 ± 1.0	99.1 ± 0.4
14	98.2 ± 0.6	98.9 ± 0.8	98.7 ± 0.7	98.1 ± 1.0	98.5 ± 0.9	98.5 ± 0.5
28	97.8 ± 0.4	98.0 ± 1.0	98.1 ± 0.9	97.5 ± 0.8	98.1 ± 1.2	97.8 ± 1.3
35	96.3 ± 0.2	96.5 ± 0.6	98.3 ± 1.0	97.1 ± 1.2	97.5 ± 0.9	98.4 ± 1.0
60	95.6 ± 0.8	94.4 ± 0.5	97.7 ± 1.2	96.9 ± 0.7	97.0 ± 1.1	98.0 ± 1.3
Hydralazine hydrochloride ^f						
1	91.3 ± 0.3	78.3 ± 3.0	97.3 ± 1.3	87.0 ± 2.9	75.8 ± 2.4	26.1 ± 4.3
2	89.3 ± 1.5	61.1 ± 4.3	96.1 ± 1.9	76.1 ± 2.6	62.6 ± 3.4	16.1 ± 1.9
7	70.6 ± 1.6	37.3 ± 2.1	88.3 ± 3.3	50.3 ± 1.9	40.4 ± 2.5	4.5 ± 3.1
10	61.8 ± 0.6	30.4 ± 1.8	81.9 ± 0.9	44.3 ± 1.4	44.4 ± 1.3	3.9 ± 2.1
14	51.1 ± 1.3	28.1 ± 3.4	78.1 ± 2.8	39.3 ± 1.8	45.3 ± 1.5	3.5 ± 1.9
28	38.3 ± 3.3	23.9 ± 2.1	65.8 ± 0.9	32.9 ± 0.9	49.2 ± 1.0	3.4 ± 1.4
35	28.7 ± 2.2	20.0 ± 1.6	62.6 ± 1.6	32.1 ± 1.1	43.3 ± 1.7	2.4 ± 2.1
60	19.6 ± 1.5	17.3 ± 2.7	48.5 ± 1.7	25.2 ± 1.5	37.6 ± 2.0	1.6 ± 2.4

^aReported as mean ± S.D. of duplicate determinations for three samples.

^bMean ± S.D. (*n* = 6) actual initial drug concentrations in the Ora-Sweet–Ora-Plus samples were 0.94 ± 0.02 mg/mL; Ora-Sweet SF–Ora-Plus, 0.99 ± 0.02 mg/mL; and cherry syrup, 1.06 ± 0.05 mg/mL.

^cMean ± S.D. (*n* = 6) actual initial drug concentrations in the Ora-Sweet–Ora-Plus samples were 15.9 ± 0.2 mg/mL; Ora-Sweet SF–Ora-Plus, 15.6 ± 0.3 mg/mL; and cherry syrup, 14.8 ± 0.3 mg/mL.

^dMean ± S.D. (*n* = 6) actual initial drug concentrations in the Ora-Sweet–Ora-Plus samples were 0.93 ± 0.04 mg/mL; Ora-Sweet SF–Ora-Plus, 0.96 ± 0.04 mg/mL; and cherry syrup, 1.01 ± 0.02 mg/mL.

^eMean ± S.D. (*n* = 6) actual initial drug concentrations in the Ora-Sweet–Ora-Plus samples were 1.11 ± 0.03 mg/mL; Ora-Sweet SF–Ora-Plus, 1.04 ± 0.02 mg/mL; and cherry syrup, 1.10 ± 0.02 mg/mL.

^fMean ± S.D. (*n* = 6) actual initial drug concentrations in the Ora-Sweet–Ora-Plus samples were 4.24 ± 0.08 mg/mL; Ora-Sweet SF–Ora-Plus, 4.12 ± 0.04 mg/mL; and cherry syrup, 3.83 ± 0.07 mg/mL.

114 days, respectively.¹⁹ Another article reported the use of enalapril maleate tablets and an isotonic citrate buffer at pH 5 to prepare 0.1- and 1.0-mg/mL oral liquids.²⁰ The drug was stable at 5 °C for 90 days, but at

25 °C enalapril maleate 0.1 and 1.0 mg/mL was stable for only 55 and 43 days, respectively. Those liquids were buffered to a pH that was 2 units less acidic than the pH at which the drug has maximum stability. The

preparations containing Ora-Plus or cherry syrup used in our study had a pH of 3.9–4.8, somewhat closer to the pH for maximum stability.

Hydralazine hydrochloride is a white to off-white or yellow, crystalline powder that is soluble to a concentration of 40 mg/mL in water and 2 mg/mL in alcohol. It has a pK_a of 7.3.²¹ The pH of a 2% aqueous solution is 3.5–4.5.²² Hydralazine hydrochloride 4 mg/mL was not stable for very long in the vehicles used in this study. At 5 °C it was stable for only one day in Ora-Sweet–Ora-Plus and for two days in Ora-Sweet SF–Ora Plus. The drug was not stable for even a day at 25 °C in these vehicles. Hydralazine hydrochloride should not be compounded in cherry syrup. Several studies have examined the stability of hydralazine hydrochloride in extemporaneously compounded preparations. Alexander et al.²³ described a formulation consisting of hydralazine hydrochloride 1.25 mg/mL in water with maltitol, edetate disodium, sodium saccharin, methylparaben, propylparaben, propylene glycol, and orange flavoring, and with acetic acid used to adjust the pH to 3.7. There was less than a 2% loss of drug at 5 °C in two weeks; the shelf-life calculated from accelerated temperature data was about five days at 25 °C. The same authors found hydralazine hydrochloride to be incompatible with edetate sodium and sodium bisulfite in an aqueous solution.

Gupta et al.²⁴ studied the stability of hydralazine hydrochloride 10 mg/mL in aqueous vehicles containing various sugars (including dextrose, fructose, lactose, and maltose). These sugars were shown to have deleterious effects on the stability of the drug, with losses of 30–70% in 24 hours in samples stored in amber bottles at 24 °C. When the drug was mixed in vehicles containing hydrolyzed sucrose in simple syrup or strawberry syrup, 93–95% of the drug was lost in one day. The authors noted that unhydrolyzed 85% sucrose solutions were more suitable vehicles for hydralazine hydrochloride 10 mg/mL; at 24 °C, there were losses of only 10% in seven days. Sorbitol solutions provided a better environment, with drug losses of only 4% and 8% in 21 days at 24 °C. The drug was stable for the longest period in 0.28 M mannitol, with no drug loss after 21 days at 24 °C.

The hydralazine hydrochloride oral liquids used in our study were prepared from the commercial tablets, which contain lactose. Lactose is a reducing sugar that can form an osazone, increasing the degradation rate of hydralazine.²⁵ It may be more appropriate to prepare only sufficient product for 24 hours at a time or to dispense the drug and the vehicle in such a manner that they can be mixed immediately before administration. One method would be to pulverize the commercial tablets and fill single doses in individual capsules. The caregiver would be instructed to empty the contents of a single capsule into one teaspoonful of vehicle for administration. Although not ideal, this may help patients.

Microbial growth was not studied.

Conclusion

Alprazolam 1 mg/mL, chloroquine phosphate 15 mg/mL, cisapride 1 mg/mL, and enalapril maleate 1 mg/mL were stable in three oral liquids compounded extemporaneously from sweetened vehicles and tablets for 60 days when stored without light at 5 and 25 °C. Hydralazine hydrochloride 4 mg/mL was stable at 5 °C for only one day in Ora-Sweet–Ora-Plus and for two days in Ora-Sweet SF–Ora-Plus.

^a2 mg-tablets, Geneva Pharmaceuticals, Inc., Broomfield, CO, lot 403JT.

^b500-mg tablets, Sanofi-Winthrop, New York, lot LA487.

^c10-mg tablets, Janssen Pharmaceuticals, Titusville, NJ, lot 94M446E.

^d20-mg tablets, Merck Sharp & Dohme, West Point, PA.

^e100-mg tablets, Rugby Laboratories Inc., Rockville Centre, NY, lot C17693.

^fPaddock Laboratories, Minneapolis, MN, lot 4C6324, containing purified water, sucrose, glycerin, sorbitol, flavoring, citric acid, sodium phosphate, methylparaben, and potassium sorbate, pH 4.2.

^gPaddock Laboratories, lot 4C6318, containing purified water, microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, flavoring, citric acid, sodium phosphate, simethicone, methylparaben, and potassium sorbate, pH 4.2.

^hPaddock Laboratories, lot 4B6257, containing purified water, glycerin, sorbitol, sodium saccharin, xanthan gum, flavoring, citric acid, sodium citrate, methylparaben, propylparaben, and potassium sorbate, pH 4.2.

ⁱRobinson Laboratory, Inc., San Francisco, CA, lot 7081010, pH 3.2 after dilution according to label instructions.

^jKerr Plastics, Memphis, TN.

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Appendix—Procedures for compounding oral liquids studied^a

Alprazolam 1 mg/mL

1. Count out 60 2-mg alprazolam tablets, and place the tablets in a mortar.
2. Comminute the tablets to a fine powder.
3. Add approximately 40 mL of the vehicle, and mix to a uniform paste.
4. Add the vehicle in geometric portions almost to volume, and mix thoroughly after each addition.
5. Transfer the contents of the mortar to a calibrated bottle.
6. Add enough vehicle to bring the final volume to 120 mL.
7. Label the bottle "Shake Well Before Using" and "Protect From Light."
8. Label the bottle with an expiration date of 60 days.

Chloroquine phosphate 15 mg/mL

1. Count out three 500-mg chloroquine phosphate tablets, and place the tablets in a mortar.
2. Comminute the tablets to a fine powder.

3. Add approximately 15 mL of the vehicle, and mix to a uniform paste.
4. Add the vehicle in geometric portions almost to volume, and mix thoroughly after each addition.
5. Transfer the contents of the mortar to a calibrated bottle.
6. Add enough vehicle to bring the final volume to 100 mL.
7. Label the bottle "Shake Well Before Using" and "Protect From Light."
8. Label the bottle with an expiration date of 60 days.

Cisapride 1 mg/mL

1. Count out 12 10-mg cisapride tablets, and place the tablets in a mortar.
2. Comminute the tablets to a fine powder.
3. Add approximately 20 mL of the vehicle, and mix to a uniform paste.
4. Add the vehicle in geometric portions almost to volume, and mix thoroughly after each addition.
5. Adjust the pH of the mixture to 7 with sodium bicarbonate.
6. Transfer the contents of the mortar to a calibrated bottle.
7. Add enough vehicle to bring the final volume to 120 mL.
8. Label the bottle "Shake Well Before Using" and "Protect From Light."
9. Label the bottle with an expiration date of 60 days.

Enalapril maleate 1 mg/mL

1. Count out six 20-mg enalapril maleate tablets, and place the tablets in a mortar.
2. Comminute the tablets to a fine powder.
3. Add approximately 15 mL of the vehicle, and mix to a uniform paste.
4. Add the vehicle in geometric portions almost to volume, and mix thoroughly after each addition.
5. Transfer the contents of the mortar to a calibrated bottle.
6. Add enough vehicle to bring the final volume to 120 mL.
7. Label the bottle "Shake Well Before Using" and "Protect From Light."
8. Label the bottle with an expiration date of 60 days.

Hydralazine hydrochloride 4 mg/mL

1. Count out four 100-mg hydralazine hydrochloride tablets, and place the tablets in a mortar.
2. Comminute the tablets to a fine powder.
3. Add approximately 15 mL of either a 1:1 mixture of Ora Sweet and Ora Plus or a 1:1 mixture of Ora Sweet SF and Ora Plus, and mix to a uniform paste.
4. Add the vehicle in geometric portions almost to volume, and mix thoroughly after each addition.
5. Transfer the contents of the mortar to a calibrated bottle.
6. Add enough vehicle to bring the final volume to 100 mL.
7. Label the bottle "Shake Well Before Using," "Protect From Light," and "Store in a Refrigerator."
8. Label the bottle with an expiration date of one day if Ora Sweet–Ora Plus was used or two days if Ora Sweet SF–Ora Plus was used.

^aExcept for the liquid containing hydralazine hydrochloride, there are three choices for the vehicle: a 1:1 mixture of Ora-Sweet and Ora-Plus, a 1:1 mixture of Ora-Sweet SF and Ora-Plus, and cherry syrup. The Ora-Sweet vehicles are products of Paddock Laboratories; the cherry syrup used in the study is a product of Robinson Laboratory, Inc.

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Stability of extemporaneous enalapril maleate suspensions for pediatric use prepared from commercially available tablets

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STABILITY OF EXTEMPORANEOUS ENALAPRIL MALEATE SUSPENSIONS FOR PEDIATRIC USE PREPARED FROM COMMERCIALY AVAILABLE TABLETS

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Abstract: In this paper, the stability of enalapril maleate in oral formulations prepared from commercially available tablets was investigated. Extemporaneously compounded, 0.1 mg/mL and 1.0 mg/mL, oral suspensions of enalapril maleate in sugar-containing and sugar-free vehicles were stored in the absence of light at 4° and 25°C for 30 days. Enalapril maleate stability was quantified after 7, 14, 21, and 30 days using HPLC method. Viscosities and pH of prepared suspensions were measured on each study day and no appreciable changes from the initial pH and initial viscosities occurred in any of the samples both at 25° and 4°C. It was shown that all the formulations retain minimum 98% of the initial enalapril maleate concentration after 30 days of storage at 25° and 4°C and they may provide an option in situations where the marketed suspension is unavailable.

Keywords: stability, enalapril maleate, oral suspension, storage, pediatric dosage form, high-performance liquid chromatography

Enalapril maleate is a pro-drug without direct biological activity which is rapidly absorbed after oral administration and de-esterified *in vivo* to its active metabolite enalaprilat, a potent angiotensin-converting enzyme inhibitor (1, 2). Enalapril maleate is widely used in pediatric cardiology – in the treatment of essential and renovascular hypertension and in congestive heart failure. The daily dose of enalapril maleate in children is in the range of 0.2-1.0 mg/kg (3-6). Enalapril maleate is currently available as 5 mg, 10 mg and 20 mg tablets and there are no commercially available suspensions for oral administration that can be used to treat younger children who are unable to swallow capsules or tablets.

The most frequent manner of prescription of enalapril maleate for infants is grounding the commercially available dosage form (tablets, capsules) into a fine powder and then packing to the capsules. Recommendations for administration in young patients involve opening capsules and mixing the powder into the liquid foods. However, accuracy of measurement and ease of administration can be problematic. The powder has an unpleasant taste and mixing them into liquid food before administration does not mask the bitter taste.

In the absence of a ready-made product, a frequent approach by pharmacists is to prepare an oral liquid from tablets or capsules. Compounded oral suspensions should be proposed as the most appropriate formulation when the tablets or capsules are prescribed for small children. During preparing suspensions from tablets or capsules one should consider a lot of important problems including: solubility and stability of the active substance, pH and composition of the suspending medium, and antimicrobial protection. The main problems appearing during preparation the formulations include achieving dose uniformity and chemical and physical stability (7). It is important that the drug should be stable in the vehicle for the proposed duration of storage and administration of the product. The characteristics of the vehicles (pH, taste, viscosity, stability, presence of preservatives) determine its suitability and compatibility for use with the drug (8).

The purpose of this study was to prepare sugar-containing and sugar-free extemporaneous oral liquid dosage form of enalapril maleate from commercially available tablets and to determine the physical and chemical stability of these products for up to 30 days.

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EXPERIMENTAL

Materials

Enalapril maleate tablets (Enarenal, 20 mg) were purchased from Polpharma S.A. (Starogard Gdański, Poland) and enalapril maleate standard was from Farmhispania (Barcelona, Spain). Methanol and hydrochloric acid were HPLC grade and purchased from Merck (Darmstadt, Germany). Citric acid was from Chempur (Piekary Śląskie, Poland) and methyl hydroxybenzoate was from Caelo Caesar & Loretz (Hilden, Germany). Hydroxyethylcellulose (Natrosol HR) was purchased from A.C.E.F. s.p.a. (Piacenza, Italy). Raspberry syrup was from Gemi (Karczew, Poland) and 85% orthophosphoric acid solution was from Fluka (Buchs, Switzerland). Water for HPLC was distilled and passed through a reverse osmosis system Milli-Q Reagent Water System (Billerica, MA, USA).

Formulations preparation

Tablets were ground to fine powder and combined with a hydroxyethylcellulose 0.5% solution (formulation A) or 1:10 mixture of raspberry syrup and hydroxyethylcellulose 0.5% solution (formulation B). Raspberry syrup masked the unpleasant taste of enalapril maleate powder. The solubility of enalapril maleate in water is 25 mg/mL at room temperature (9). Enalapril maleate has pK_a values of 3.0 and 5.4. The maximum stability of enalapril maleate is at a pH of ~ 3 (10), and therefore the pH value of prepared formulations was adjusted to 3.0 using cit-

ric acid (1 M). Initial enalapril maleate concentrations in suspension were: 0.1 mg/mL and 1.0 mg/mL. All suspensions contained methyl hydroxybenzoate 0.2% as a preservative. The product was filled in separated 200-mL orange glass bottles and stored at $4^{\circ} \pm 2^{\circ}\text{C}$ and at $23^{\circ} - 25^{\circ}\text{C}$, in the absence of light. Before removing samples, the containers were agitated to ensure uniform resuspension of insoluble materials.

Instrumentation and chromatographic conditions

The HPLC system consisted of an Agilent Technologies 1200 series instruments equipped with a G1312A binary pump, a G1316A thermostat, a G1379B degasser and a G1315B diode array detector (Agilent, Waldbronn, Germany). Data collection and analysis were performed using Chemstation 6.0 software (Agilent, Waldbronn, Germany). The experimental method was modified according to that previously reported (11-13). Separation was achieved on a C18 Spherisorb column 4.6×250 mm ODS2, 5 μm (Waters, Dublin, Ireland). Mobile phase was methanol/water (5:95, v/v) (pH 2.5), the flow rate was 1.0 mL/min and UV detection was performed at a wavelength of 215 nm. pH of the mobile phase was adjusted to 2.5 by using 10% orthophosphoric acid solution. The column temperature was maintained at 25°C . For injection into the HPLC system 50 μL of sample was used. All reagents used for analysis were of HPLC grade.

Calibration standards of 1.0 mg/mL stock solution of enalapril maleate (standard powder) in hydrochloric acid (0.1 M) were prepared.

Table 1. Stability of enalapril maleate 0.1 mg/mL and 1.0 mg/mL in sugar-free (formulation A) and sugar-containing (formulation B) vehicles stored at 25°C and 4°C .

Formulation/ Temperature	Initial ^a concentration (mg/mL)	% Initial concentration remaining ^a			
		Day 7	Day 14	Day 21	Day 30
A					
25°C	0.1 ± 0.02	99.6 ± 0.3	99.2 ± 0.6	99.3 ± 0.4	98.2 ± 0.9
4°C	0.1 ± 0.02	99.4 ± 0.4	99.4 ± 0.4	99.3 ± 1.2	99.1 ± 1.0
25°C	1.0 ± 0.04	99.4 ± 0.8	101.2 ± 0.7	98.3 ± 1.0	98.4 ± 0.8
4°C	1.0 ± 0.04	98.9 ± 1.1	99.4 ± 0.3	98.5 ± 0.8	98.0 ± 0.9
B					
25°C	0.1 ± 0.01	99.5 ± 0.4	99.6 ± 0.4	99.3 ± 0.2	99.4 ± 0.4
4°C	0.1 ± 0.01	99.7 ± 0.9	99.3 ± 0.5	98.4 ± 0.5	98.3 ± 0.5
25°C	1.0 ± 0.03	99.2 ± 0.5	99.4 ± 0.6	99.1 ± 1.1	99.1 ± 0.6
4°C	1.0 ± 0.03	99.4 ± 0.4	99.4 ± 0.6	99.1 ± 0.7	98.2 ± 0.8

^a The mean values ± S.D. from three independent experiments done in duplicate are presented

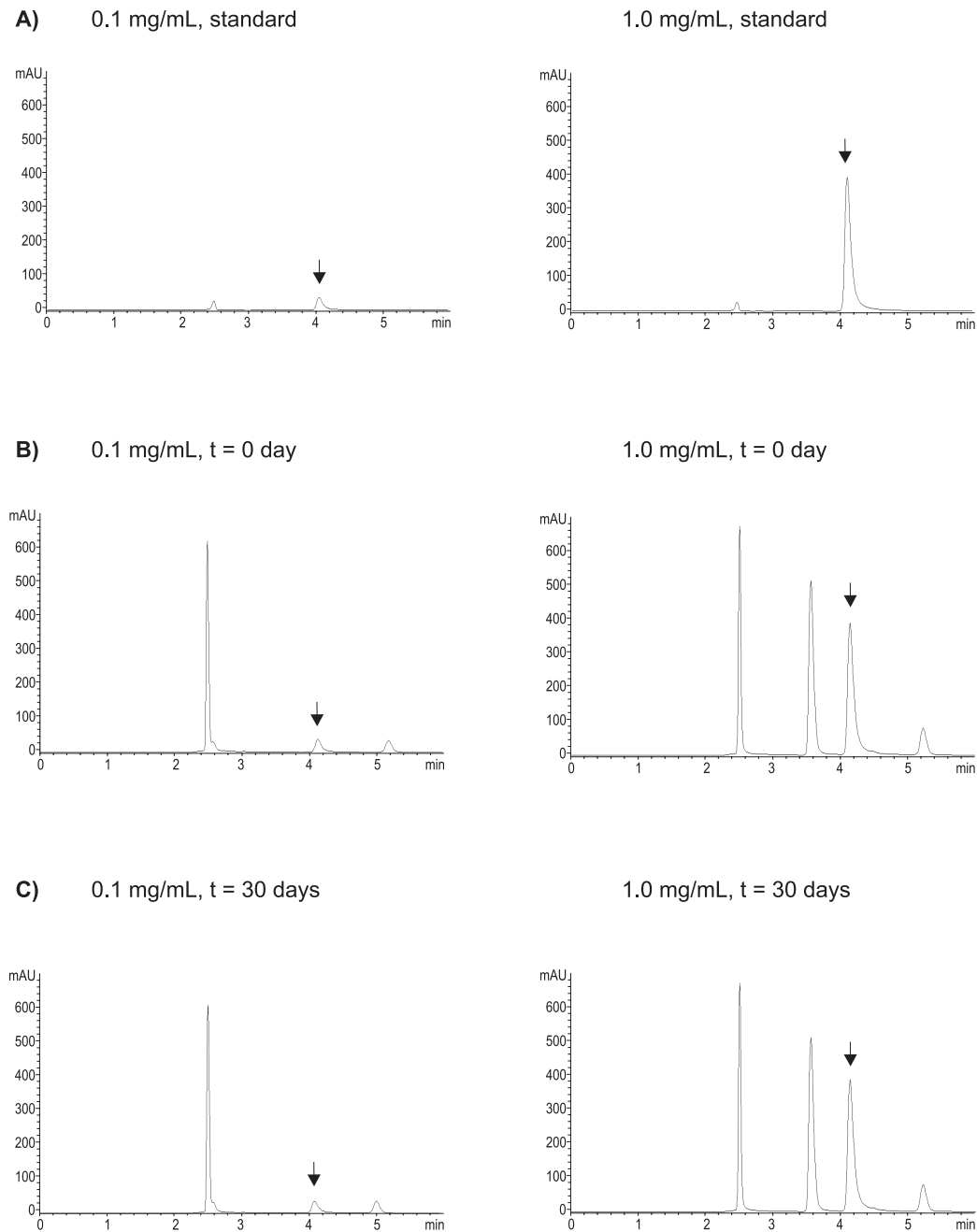


Figure 1. The representative chromatograms of enalapril maleate 0.1 mg/mL and 1.0 mg/mL in formulation B: standards (A), at time 0 (B) and stored for 30 days at 25°C (C). Enalapril maleate retention time = 4.120 min. Arrows indicate enalapril peaks.

Calibrations standard solutions at five levels were prepared by diluting the stock solution for the analytical range of 0.005-0.1 mg/mL. Volumes of 50 μ L of this standards were injected to obtain calibration curve. Standard curve was produced by the software included in the HPLC system and it was linear with the r^2 values greater than 0.999.

Stability examination (Enalapril maleate analysis)

Enalapril maleate stability was quantified after 7, 14, 21, and 30 days. Ten mL samples of each formulations were centrifuged at 3800 rpm for 20 min to sediment insoluble excipients. Aliquots of supernatant were diluted 1:10 with hydrochloric acid (0.1

Table 2. pH of enalapril maleate 0.1 mg/mL and 1.0 mg/mL in sugar-free (formulation A) and sugar-containing (formulation B) vehicles stored at 25°C and 4°C.

Formulation/ Temperature	Concentration (mg/mL)	pH ^a	
		Day 0	Day 30
A			
25°C	0.1	3.00 ± 0.03	3.02 ± 0.05
4°C	0.1	3.00 ± 0.04	2.98 ± 0.02
25°C	1.0	3.05 ± 0.02	3.10 ± 0.02
4°C	1.0	3.05 ± 0.02	3.10 ± 0.03
B			
25°C	0.1	3.05 ± 0.01	3.09 ± 0.02
4°C	0.1	3.05 ± 0.03	3.04 ± 0.04
25°C	1.0	3.04 ± 0.03	3.10 ± 0.01
4°C	1.0	3.04 ± 0.02	3.03 ± 0.03

^a The mean values ± S.D. from three independent experiments done in duplicate are presented

Table 3. Viscosity [mPa·s] of enalapril maleate 0.1 mg/mL and 1.0 mg/mL in sugar-free (formulation A) and sugar-containing (formulation B) vehicles stored at 25°C and 4°C.

Formulation/ Temperature	Concentration (mg/mL)	Viscosity (mPa·s) ^{aa}	
		Day 0	Day 30
A			
25°C	0.1	109 ± 2.0	106 ± 2.0
4°C	0.1	109 ± 2.0	110 ± 3.0
25°C	1.0	115 ± 3.0	113 ± 2.0
4°C	1.0	115 ± 3.0	118 ± 3.0
B			
25°C	0.1	103 ± 3.0	100 ± 2.0
4°C	0.1	103 ± 3.0	103 ± 3.0
25°C	1.0	110 ± 1.0	106 ± 3.0
4°C	1.0	110 ± 1.0	114 ± 2.0

^a The mean values ± S.D. from three independent experiments done in duplicate are presented

M), filtered through a 0,45 µm CA membrane filter (Witko, Łódź, Poland) and injected into the HPLC system. Replicate injections were made for all samples.

The stability of enalapril maleate in all formulations was determined by calculating the percentage of the initial concentration remaining at each time interval. Stability was defined as the retention of not less than 90% of the initial concentration (14).

pH examination

The apparent pH was determined initially (day 0) and on each study day. Examination was conducted with pH-meter CP-401 (Elmetron, Zabrze, Poland). pH of each sample was measured six times and then the results were averaged.

Viscosity determination

To determine if storage period at 4°C and 25°C had an effect on viscosity of enalapril maleate suspensions, they were subjected to shear stress in a rotational viscometer Viscotester 6 Plus (Thermo Haake, Karlsruhe, Germany). Viscosity, which is the inverse of fluidity, was measured in units of milliPascal × seconds (mPa·s).

Viscosity measurements of 15 mL aliquots of each suspension were taken initially (day 0) and on each study day. Samples were subjected to a constant shear rate 100 min⁻¹ for 60 s. Preliminary experiments had shown that viscosity became constant for preparations analyzed in this study 60 s into the run. Therefore, viscosities reported here are those recorded at 60 s. Viscosity of the suspensions

was measured six times and the results were averaged.

Statistical analysis

The results were analyzed by analysis of variance (ANOVA) and multiple comparison were done to check statistical significance. The data were expressed as the mean value for 3 independent assays in duplicate \pm S.D. The statistical significance between means was verified by Sheffe's comparison test accepting $p < 0.05$ as significant.

RESULTS AND DISCUSSION

A large number of drugs are prepared extemporaneously by pharmacists as oral liquid dosage forms. Pediatric oral formulations can be quite scientifically challenging to develop and the prerequisites for both measurable dosage form to administer based upon body-weight, and also taste-masking are two of the challenges unique for pediatric oral formulations. Extemporaneous compounding of this type usually involves preparing an oral liquid from a commercially available dosage form. It is important that the drug must be stable in the vehicle for the proposed duration of storage and administration of the product. Each vehicle possesses unique physico-chemical characteristics that determine its suitability for use with various drugs. These characteristics include pH, viscosity, taste, appearance, presence of preservatives, and stability. There are several studies concerning the stability of enalapril maleate, which were conducted in USA (15, 16) and other countries (17). In these examinations, the stability of enalapril maleate in deionized water, citrate buffer solution and carboxymethylcellulose as a suspending agent was studied. In our work the stability of enalapril maleate in oral suspensions made from tablets of Polish producer was examined. All the suspensions contained methyl hydroxybenzoate 0.2% as a preservative, hydroxyethylcellulose as the suspending agent and citric acid as the pH adjusting agent.

The stability of enalapril maleate in concentration of 0.1 mg/mL and 1.0 mg/mL in oral suspensions was studied by modified HPLC method (11-13). The results obtained in this work confirmed that enalapril maleate was stable in suspensions stored both at 25°C and 4°C. All suspensions showed only 1% – 2% degradation after 30 days of storage, which fulfilled the USP criterion (14). Figure 1 exhibits representative chromatograms obtained from samples of formulation **B** stored for 30 days at 25°C. Refrigerated and stored at room temperature formulations **A** and formulations **B** retained more than

98% of their initial enalapril maleate concentrations. There were no evident changes in enalapril maleate stability evoked by sugar (Table 1). Enalapril maleate stability was also examined under stressed conditions (autoclaved three times at $121 \pm 2^\circ\text{C}$) and no additional peaks of degradation products was observed.

It was shown that storage conditions did not influence the suspensions pH in significant way. No appreciable change from the initial pH (3.0) occurred in any of the samples both at 25°C and 4°C (Table 2). The pH examination of all formulations stored at 25° and 4°C showed only less than 0.1 pH unit change throughout the study. The data in Table 2 showed that enalapril maleate pH is stable after one month storage.

Viscosity was measured in order to determine if the temperature of storage had an effect on the viscosity. Refrigerated suspensions demonstrated higher viscosity than suspensions stored at 25°C but prolonged refrigeration did not increase the suspensions' viscosities in significant manner. It was likewise noted that addition of the raspberry syrup (formulation **B**) slightly lowered the viscosity of enalapril maleate suspensions in concentrate of 0.1 and 1.0 mg/mL stored either at 25°C or at 4°C (Table 3). Viscosity of the analyzed enalapril maleate suspensions was in the range of viscosities of the commercially available pediatric oral suspensions.

The tablet suspension in water would be expected to readily support microbial growth, especially at room temperature during in-use conditions, therefore 0.2% methyl hydroxybenzoate as compatible with the drugs preservative was added (17). No colonies or other evidence of bacterial or fungal growth were detected for any of the formulations tested. There was also no detectable change in color, odor, and taste in any sample. However, in the absence of microbiological data, the shelf-life given to extemporaneous products containing preservatives is usually 30 days – the time period in which the formulations were tested.

The obtained data suggest that these formulations may provide an option in situations where the marketed suspension is unavailable.

CONCLUSION

Extemporaneously compounded enalapril maleate 0.1 mg/mL and 1.0 mg/mL oral suspensions, in sugar-containing and sugar-free vehicles, were stable for at least 30 days when stored at 4° and 25°C. The viscosities and pH of all tested formula-

tions did not significantly change over 30 days. All the formulations retain minimum 98% of the initial enalapril maleate concentration after 30 days of storage at 4° and 25°C and may provide flexible and convenient dosage forms for pediatric patients.

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Stability of enalapril maleate in three extemporaneously prepared oral liquids

MILAP C. NAHATA, RICHARD S. MOROSCO, AND THOMAS F. HIPPLE

Abstract: The stability of enalapril 1 mg/mL (as the maleate) in deionized water, citrate buffer solution, and a sweetened suspending agent at two temperatures was studied.

Twenty enalapril 10-mg tablets were crushed to a powder. Deionized water, citrate buffer solution, or sweetened vehicle was added to produce three 200-mL batches of each liquid; the expected final concentration of

enalapril in each was 1 mg/mL. Each formulation was stored in 10 60-mL bottles, 5 of which were stored at 4 °C and 5 at 25 °C. Samples were collected on days 0, 7, 14, 28, 42, 56, 70, and 91 for visual inspection and analysis by high-performance liquid chromatography; pH was measured at each sampling time as well.

The mean concentration of enalapril in the three liquids at 4 °C was >94% of the ini-

tial concentration throughout the 91-day study period. At 25 °C, the mean concentration of enalapril was >90% for 56 days and >92% for 91 days in both citrate buffer solution and sweetened vehicle. The pH of the liquid prepared with deionized water and stored at 25 °C decreased by 2.0 pH units.

Enalapril 1 mg/mL (as the maleate) in three extemporaneously compounded oral liquids was stable for 91 days

at 4 and 25 °C with the exception of enalapril in deionized water, which was stable for only 56 days at 25 °C.

Index terms: Buffers; Cardiac drugs; Citric acid; Compounding; Enalapril maleate; Incompatibilities; Stability; Storage; Suspending agents; Suspensions; Sweetening agents; Tablets; Temperature; Vehicles; Water
Am J Health-Syst Pharm. 1998; 55:1155-7

Enalapril maleate is frequently used in infants and young children for the treatment of hypertension and congestive heart failure. It is commercially available as 2.5-, 5-, 10-, and 20-mg tablets. The initial dosage is usually 0.1 mg/kg/day for infants and

children.¹ No liquid dosage form is commercially available for pediatric patients. In addition, there are limited data on the stability of enalapril in extemporaneously prepared oral liquids.

Boulton et al.² found enalapril 0.1 and 1 mg/mL (as

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Reports Enalapril maleate

the maleate) to be stable for at least 30 days at 5 °C in a solution of isotonic citrate buffer solution (pH 5). However, there are no known stability data for enalapril in readily available vehicles such as carboxymethylcellulose in syrup. Our study was designed to determine the stability of enalapril maleate in deionized water, citrate buffer solution, and a sweetened suspending agent at 4 and 25 °C.

Methods

Twenty enalapril maleate 10-mg tablets^a were used to prepare three 200-mL batches of each liquid. In each case the tablets were crushed to powder by using a mortar and pestle, and the powder was mixed with deionized water^b; citric acid buffer, pH 5^c; or a 1:1 mixture of Ora-Sweet^d and Ora-Plus^e (appendix). None of the liquids was filtered to remove insoluble excipients. The nominal final concentration of enalapril in each liquid was 1 mg/mL.

Each of the enalapril formulations was stored in 10 60-mL plastic prescription bottles.^f Five bottles of each formulation were stored at 4 °C in a refrigerator,^g and the other five bottles were stored at 25 (±1) °C in a temperature-controlled water bath.^h After thorough shaking, a 0.5-mL sample was collected from each bottle on days 0, 7, 14, 28, 42, 56, 70, and 91, visually examined, and analyzed in duplicate by a high-performance liquid chromatographic (HPLC) method.² The pH was measured at each sampling time as well.

The HPLC instrumentation consisted of a pump, an autosampler, and a variable-wavelength ultraviolet-light detectorⁱ; an integrator^j; and a C₈ column.^k A digital pH meter,^l a wrist-action shaker,^m and a Vortex mixerⁿ were also used. The mobile phase consisted of 65% 20 mM potassium phosphate monobasic^o and 35% acetonitrile.^p Before use, the mobile phase was passed through a 0.45-μm nylon 66 filter^q and then degassed with helium. The flow rate was 1 mL/min. The detector was set at 215 nm, and the injection volume was 10 μL. The column was maintained at 80 °C. The chemicals and reagents, including phosphoric acid,^r buffer solution pH 7,^s buffer solution pH 4,^t and buffer solution pH 10,^u were American Chemical Society or analytical grade. Under these conditions, enalapril eluted at 2.9 minutes.

A stock solution of enalapril reference standard^v was prepared in water and diluted to yield concentrations of 1.5, 1.25, 1, 0.75, 0.5, and 0.1 mg/mL. One hundred microliters of each of these solutions was then mixed with 900 μL of mobile phase and analyzed, as were the samples.

In order to establish the stability-indicating nature of the method, enalapril in water was forcibly degraded by acid^w and base^x hydrolysis and oxidation^y at 60 °C. The sample was processed as described earlier. The peaks for the degradation products appeared at 1.2, 4.6, and 7.8 minutes and did not interfere with the quanti-

tation of enalapril. Chromatograms of the oral liquids without enalapril were compared with chromatograms of enalapril standard; constituents of the oral liquids were found not to interfere with the measurement of enalapril. Linearity of the standard curve was determined by linear regression analysis of the enalapril concentrations (0.1–1.5 mg/mL) versus peak height of enalapril; the correlation coefficient was greater than 0.999. The accuracy of the method ranged from 99.2% to 101.6%, and the interday and intraday coefficients of variation were less than 4%.

Enalapril was considered stable if its concentration after storage was ≥90% of the initial concentration.

Results

At 4 °C, the mean concentration of enalapril in the three liquids was >94% of the initial concentration throughout the 91-day study period, but at 25 °C, the mean concentration was >90% for 56 days in deionized water and >92% for 91 days in both citrate buffer solution and the sweetened suspending agent (Table 1). The physical appearance of the liquids remained unchanged, and pH did not change by more than 0.1 pH unit except in the liquid prepared with deionized water and stored at 25 °C, in which case pH decreased by 2.0 pH units.

Table 1.
Stability of Enalapril 1 mg/mL at 4 and 25 °C

Day	% Initial Concentration Remaining ^a		
	Deionized Water	Citrate Buffer Solution pH 5.0	1:1 Mixture of Ora-Plus and Ora-Sweet ^b
At 4 °C			
0	100.0 ± 1.0 ^c	100.0 ± 1.2 ^d	100.0 ± 3.6 ^e
7	98.6 ± 1.3	98.7 ± 1.6	99.4 ± 4.8
14	98.1 ± 1.4	99.1 ± 1.9	98.6 ± 5.3
28	97.6 ± 1.9	98.7 ± 2.0	98.4 ± 5.9
42	97.1 ± 1.9	98.5 ± 1.3	97.9 ± 4.2
56	96.5 ± 1.1	97.3 ± 1.2	96.9 ± 5.0
70	95.2 ± 1.3	96.3 ± 2.2	96.1 ± 5.3
91	94.8 ± 1.8	95.9 ± 1.3	95.8 ± 5.9
At 25 °C			
0	100.0 ± 1.0 ^f	100.0 ± 1.2 ^g	100.0 ± 3.3 ^h
7	98.3 ± 1.4	98.2 ± 1.8	99.7 ± 5.2
14	96.4 ± 2.1	97.0 ± 1.9	98.1 ± 5.9
28	94.1 ± 3.3	95.8 ± 2.5	96.2 ± 6.3
42	92.4 ± 2.4	95.3 ± 1.8	96.2 ± 4.4
56	90.1 ± 3.5	94.9 ± 2.6	95.7 ± 5.2
70	87.6 ± 4.1	93.9 ± 2.4	94.4 ± 5.7
91	84.1 ± 4.7	92.7 ± 2.7	93.8 ± 6.1

^aMean ± S.D. of duplicate determinations for five samples.

^bPaddock Laboratories.

^cThe actual mean ± S.D. initial concentration was 0.99 ± 0.06 mg/mL, and the initial pH was 7.1.

^dThe actual mean ± S.D. initial concentration was 0.99 ± 0.01 mg/mL, and the initial pH was 5.1.

^eThe actual mean ± S.D. initial concentration was 1.01 ± 0.04 mg/mL, and the initial pH was 4.7.

^fThe actual mean ± S.D. initial concentration was 0.97 ± 0.02 mg/mL, and the initial pH was 7.1.

^gThe actual mean ± S.D. initial concentration was 0.98 ± 0.03 mg/mL, and the initial pH was 5.1.

^hThe actual mean ± S.D. initial concentration was 0.99 ± 0.01 mg/mL, and the initial pH was 4.7.

Discussion

The formulation with deionized water would be the least expensive of the three formulations to prepare and its vehicle the most accessible. However, if a suspending agent with a sweetener is desired, enalapril can be prepared with equal volumes of commercially available Ora-Plus and Ora-Sweet.

Because of the lack of stability data, some doses of enalapril maleate have been dispensed as a powder prepared by diluting crushed tablets with lactose. This practice is cumbersome and labor-intensive, however. The knowledge that enalapril maleate is stable in widely available vehicles should simplify the preparation and delivery of weight-specific doses to infants and young children.

Conclusion

Enalapril 1 mg/mL (as the maleate) in three extemporaneously compounded oral liquids was stable for 91 days at 4 and 25 °C with the exception of enalapril 1 mg/mL in deionized water, which was stable for only 56 days at 25 °C.

^aMerck & Co. Inc., West Point, PA, lot B2698.

^bDeionized water type I, Children's Hospital, Columbus, OH.

^cChildren's Hospital, lot C139601MMCH.

^dPaddock Laboratories, Minneapolis, MN, lot 5K6734, containing purified water, sucrose, glycerin, sorbitol, flavoring, citric acid, sodium phosphate, methylparaben, and potassium sorbate, pH 4.2.

^ePaddock Laboratories, lot 4E6462, containing purified water, microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, flavoring, citric acid, sodium phosphate, simethicone, methylparaben, and potassium sorbate, pH 4.2.

^fOI Owens-Illinois, Toledo, OH.

^gWhite-Westinghouse, White Consolidated Inc., Columbus, OH.

^hLauda RM20, Brinkmann Instruments, Inc., Westbury, NY.

ⁱHP 1050 series, Hewlett-Packard Co., Analytical Products Group, Palo Alto, CA.

^jHP 3396A, Hewlett-Packard.

^kZorbax Reliance C₈ column, 5 µm, 4.0 × 160 mm, MAC-MOD Analytical, Chadds Ford, PA.

^lModel 701A, Orion Research Inc., Boston, MA.

^mBurrell Corp., Pittsburgh, PA.

ⁿVortex Genie 2, Fisher Scientific, Pittsburgh, PA.

^oSigma Chemical Co., St. Louis, MO, lot 16H1604.

^pBurdick & Jackson, Division of Baxter, Muskegon, MI, lot BL893.

^qGelman Sciences, Ann Arbor, MI, lot 0082205.

^rMallinckrodt Inc., Science Products Division, St. Louis, MO, lot 2796 KESK.

^sFisher Scientific, lot 91090-24.

^tFisher Scientific, lot 910043-23.

^uFisher Scientific, lot 906524-24.

^vUnited States Pharmacopeial Convention, Inc., Rockville, MD, lot H1.

^wHydrochloric acid, Mallinckrodt Specialty Chemical Co., Chesterfield, MO, lot AB12KBSV.

^xSodium hydroxide, Aldrich Chemical Co., Milwaukee, WI, lot 0011ODY.

^yHydrogen peroxide, Aldrich Chemical, lot 05427TX.

References

1. Taketomo CK, Hodding JH, Kraus DM. Pediatric dosage handbook. 4th ed. Hudson, OH: Lexi-Comp; 1997-98:276-8.
2. Boulton DW, Woods DJ, Fawcett JP et al. The stability of an enalapril maleate oral solution prepared from tablets. *Aust J Hosp Pharm.* 1994; 24:151-6.

Appendix—Procedure for compounding enalapril maleate oral liquid

1. Count out 20 10-mg enalapril tablets.
2. Crush the tablets in a mortar.
3. Add a small volume of the vehicle,^a and triturate to make a smooth paste.
4. Add increasing volumes of the vehicle to make the enalapril liquid pourable.
5. Transfer the liquid to a graduated cylinder.
6. Add enough vehicle to bring the final volume to 200 mL.
7. Label the bottle "Shake Well Before Using" and "Protect From Light."
8. Label with an expiration date: 91 days if prepared with citrate buffer solution or sweetened suspending agent; 91 days if prepared with deionized water for storage in the refrigerator; 56 days if prepared with deionized water for storage at room temperature.

^aUse deionized water, citrate buffer solution, or a commercial sweetened suspending agent. Prepare the isotonic citrate buffer solution (pH 5.0) by dissolving 0.353 g of Citric Acid Monohydrate Granular, USP, 1.01 g of Sodium Citrate Dihydrate Granular, USP, and 0.54 g of sodium chloride in 100 mL of distilled water. Prepare the sweetened suspending agent by mixing equal volumes of Ora-Plus and Ora-Sweet (Paddock Laboratories).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Examiner: Stephanie K. Springer
Serial No.: 15/081,603	Confirmation No.: 3892
Filed: March 25, 2016	Customer No.: 021971
Title: ENALAPRIL FORMULATIONS	

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132

I, **Gerold Mosher**, do hereby declare as follows:

1. I am currently employed at Silvergate Pharmaceuticals, Inc.
2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.
3. I have been employed at Silvergate Pharmaceuticals since 2013, as Vice President of Drug Development. As part of my job duties, I develop oral solutions for pediatric use. I have a small laboratory where I develop, characterize and move formulations through the steps required for FDA approval and eventual sale.
4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also



been employed by small startup companies to develop new solubilizing technology for oral, injectable and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for almost 38 years, and have extensive experience in developing pharmaceutical formulations. My Curriculum Vitae is attached as Exhibit A.

6. I am familiar with the subject matter claimed in patent application 15/081,603, and am a named inventor on this application. Silvergate Pharmaceuticals is also the Assignee of the '603 application.

7. I am aware of the Non-Final Office Action mailed in this matter on January 17, 2017. I am also aware that the oral enalapril liquid formulation claims stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over US 8,568,747, Nahata et al. (Stability of Enalapril Maleate in three Extemporaneously Prepared Oral Liquids) ("Nahata"), Product Information of Bicitra (Sodium Citrate and Citric Acid Oral Solution) ("Bicitra"), Product Information of Ora-Sweet ("Ora-sweet"), and Rippley et al. (Pharmacokinetics Assessment of an Oral Enalapril Suspension for Use in Children) ("Rippley"). I have reviewed these cited references in the Non-Final Office Action.

8. I am submitting this declaration to address the comments made in the Office Action.

9. The '603 application relates to enalapril oral liquid formulations that are stable for least 12 months at 5 ± 3 °C. The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water at a pH of less than 3.5. Development of this described enalapril formulation was oriented on preparing a safe, stable, soluble oral liquid with minimal degradation and having acceptable taste for pediatric patients.

10. The currently approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in "Nahata" and subsequently administering the suspension to the

patient, or (3) reconstituting a powder in a liquid carrier, such as the described enalapril powder in US 8,568,747.

11. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty in swallowing oral dosage forms. For the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination. Similarly, reconstituting powders into a liquid carrier also requires an extra step and could introduce variability, solubility and contamination issues during the reconstitution.

12. As compared to these currently available methods, the enalapril oral liquid formulations claimed in the '603 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

13. It should be appreciated that the oral enalapril liquid formulations of the present claims are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

14. Evidence of this stability is found in exemplary formulations E7 and E8 which show minimal degradation as compared to current formulations. In this study, exemplary formulations E7 and E8 were stored at either refrigerated condition (5 °C) or at ambient condition (25 °C). Formulations details for E7 and E8 are as follows:

Composition of Enalapril Maleate Formulations		
Component	E7	E8
Enalapril maleate	1.00	1.00
Citric acid anhydrous	1.80	1.82
Sodium citrate anhydrous	0.16	0.15
Sodium benzoate	1.00	1.00
Sucralose	0.70	0.70
Mixed berry flavor	0.50	0.50
Water	qs	qs
pH (measured)	3.3	3.3

qs = sufficient quantity

15. In my review of the references cited in the Office Action, none of the references describe this stability of at least 12 months at 5 ± 3 °C or any means of achieving this stability for enalapril formulations.

16. I have reviewed Nahata which describes the extemporaneous preparation of oral liquid enalapril formulations by crushing enalapril tablets with a mortar and pestle and suspending the resulting ground tablets in water, citrate buffer, or Ora-Plus/Ora-Sweet. On stability, Nahata states that the “compounded oral liquids [were] stable for 91 days at 4 and 25 °C” defining stable as “concentration after storage was $\geq 90\%$ of the initial concentration. Table 1 of Nahata shows that the enalapril extemporaneous formulations exhibited about 5% loss of enalapril after about 56 days at 4 °C and about 5% loss of enalapril after about 91 days at 25 °C.

17. I have also reviewed US 8,568,747 which describes an oral liquid enalapril formulation obtained by reconstituting an enalapril powder in a liquid. The table in example 6 of US 8,568,747 shows that the resulting oral liquid formulation exhibited about 5% loss of enalapril after about 8 weeks at 25 °C.

18. I additionally reviewed Bicitra, Ora-sweet, and Rippley and they do not provide any stability of enalapril formulations whatsoever.

19. To compare the stability of the enalapril extemporaneous preparations as described in Nahata and the reconstituted liquid formulation of US 8,568,747, I submit the following data which depicts the enalapril content of formulations E7 at 5°C and 25 °C and E8 at 5 °C in Table A and Table B:

Table A: Enalapril content in formulations after storage at 5 °C¹

	Nahata				
Days	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	E7	E8
0	100	100	100	100	100
7	98.6	98.7	99.4		
14	98.1	99.1	98.6		
28	97.6	98.7	98.4		
40				100.9	
42	97.1	98.5	97.9		100.3
56	96.5	97.3	96.9		
70	95.2	96.3	96.1		
91	94.8	95.9	95.8		
99				104.7	
205				101.1	
290				101.0	
383				99.7	
581				99.1	

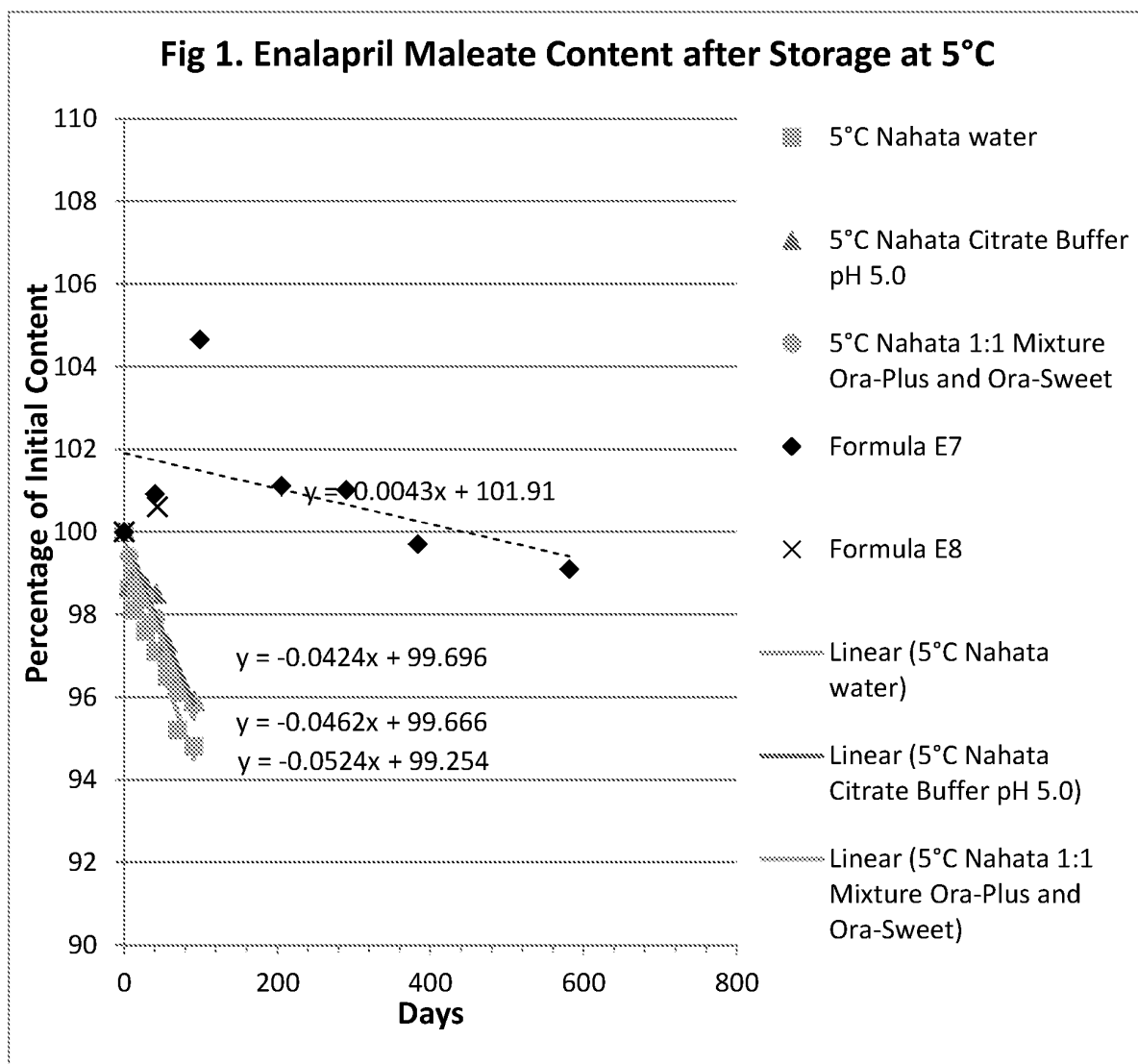
Table B: Enalapril content in formulations after storage at 25 °C

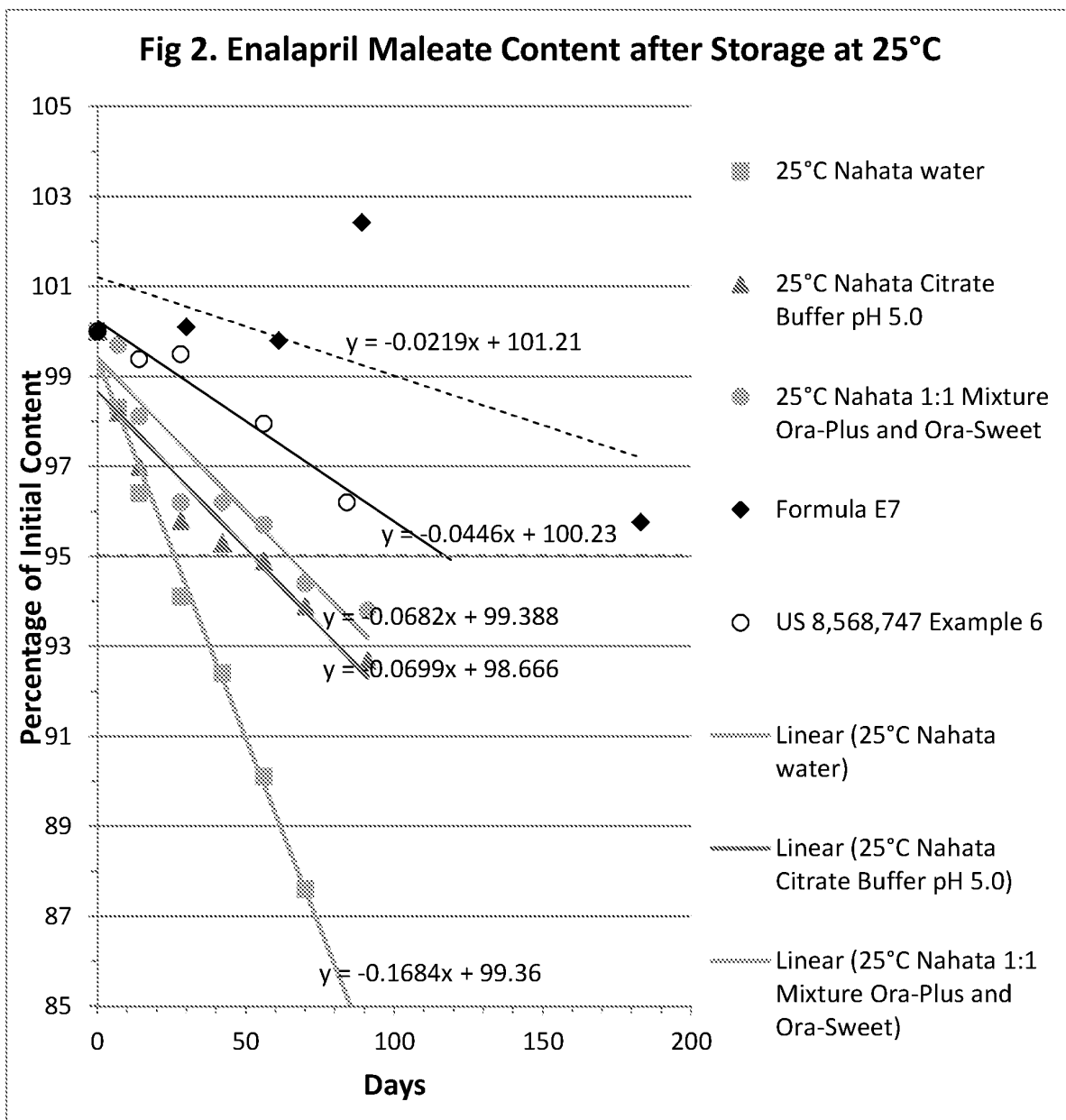
	Nahata			US 8,568,747	
Days	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	Example 6	E7
0	100	100	100	100	100
7	98.3	98.2	99.7		
14	96.4	97	98.1	99.4	
28	94.1	95.8	96.2	99.5	
30					100.1
42	92.4	95.3	96.2		
56	90.1	94.9	95.7	97.9	
61					99.8

¹ I note that US 8,568,747 does not provide stability data of the reconstituted liquid formulation at 5 °C.

70	87.6	93.9	94.4		
84				96.2	
89					102.4
91	84.1	92.7	93.8		
183					95.8

20. To further describe the contrast in stability, the enalapril concentrations published by Nahata, the US 8,568,747 enalapril concentrations, and the concentrations from E7 and E8 are plotted graphically (Fig. 1: 5 °C and Fig. 2: 25 °C) with linear regression of the data for extrapolation.





21. Table A and Fig. 1 show that E7 exhibits excellent stability for at least 18 months (581 days) at 5 °C with essentially no loss of enalapril content in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at 5 °C for more than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.

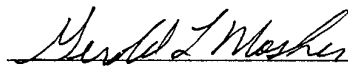
Attorney Docket No.: 43060-707.201

22. Table B and Fig. 2 show that E7 also exhibits better stability for at least 6 months (183 days) at 25 °C in contrast to the Nahata preparations and the reconstituted formulation of US 8,568,747.

23. The additional enalapril content data submitted for E7 and E8 shows that the formulations of the present application are significantly more stable, which in my opinion reflects the superior results and advantages, obtained with the oral liquid enalapril formulation of the present claims.

24. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under 18 U.S.C. 1001.

Respectfully submitted on this 2nd day of February, 2017

A handwritten signature in cursive script, appearing to read "Gerold L. Mosher", is written over a horizontal line.

Gerold L. Mosher, Ph.D.

Attorney Docket No. 43060-707.304

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 3572
Serial No.: 16/177,159	Examiner: SPRINGER, Stephanie K
Filed: October 31, 2018	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on May 15, 2020, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: _____/Paula Derby/</p>

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132

I, **Gerold Mosher**, state and declare as follows:

1. I am currently employed at Azurity Pharmaceuticals, Inc., a company formed in May 2019 by the acquisition of Silvergate Pharmaceuticals, Inc. by CutisPharma, Inc.
2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.
3. I have been employed at Silvergate Pharmaceuticals and now Azurity Pharmaceuticals since 2013, and my current position is Vice President of Product Development. As part of my job duties, I develop oral formulations for pediatric use. I have a small laboratory where I



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develop, characterize and move formulations through the steps required for FDA approval and eventual sale.

4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also been employed by small startup companies to develop new solubilizing technology for oral, injectable, and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for about 40 years, and have extensive experience in developing pharmaceutical formulations. My *Curriculum Vitae* is attached as Exhibit A.

6. I am familiar with the subject matter claimed in U.S. Pat. App. Ser. No. 16/177,159 (“the ’159 application”), and I am a named inventor on this application. Silvergate Pharmaceuticals, Inc. is the assignee of all rights in the invention of the pending ’159 application.

7. I am aware of the Non-Final Office Action mailed in this matter on January 7, 2020. I am also aware that the pending claims were rejected under 35 U.S.C. 112(b) and 35 U.S.C. 112(a).

8. I am submitting this declaration to address some of the comments made in the Office Action,.

9. The ’159 application relates to enalapril oral liquid formulations that are stable at about 5 ± 3 °C for at least 12 months. The development of this described enalapril formulation was oriented on preparing a safe, stable, uniform oral liquid with minimal degradation and having an acceptable taste for pediatric patients.

10. Traditionally, approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in “Nahata” and subsequently administering the suspension to the patient, or (3) reconstituting a powder in a liquid carrier. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty swallowing solid oral dosage forms. For the second method,

extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination.

11. Compared to these currently available methods, the enalapril oral liquid formulation claimed in the '159 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

12. The oral enalapril liquid formulations of the '159 application have superior stability—they are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

13. The '159 application describes that stable oral enalapril liquid formulations can be prepared with suitable buffers including citrate buffers at varying concentrations. Formulations containing a mixture of citric acid and sodium citrate at various amounts as buffers are exemplified in the '159 application, for example, formulations B1-B3 in Example B and formulations E1-E6 in Example E. The buffer concentrations of formulations E1 to E6 are the following:

Buffer Concentration	E1	E2	E3	E4	E5	E6
----------------------	----	----	----	----	----	----

Citric acid (mg/mL)	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate (mg/mL)	0.75	0.75	0.75	0.75	0.38	0.19
Citrate concentration (mM)	20	20	20	20	10	5

14. The storage stability of formulations E1-E6 is summarized in Table E-2, partially copied below for the stability results at 5 °C. After storing at about 5 °C for a period of 52 or 62 weeks, the combined amount of two primary degradants, Enalaprilat and diketopiperazine, remained less than 1 % w/w, demonstrating excellent formulation stability. As shown in Table E-2, the formulations prepared with 5 mM, 10 mM or 20 mM of a mixture of citric acid and sodium citrate as a buffer have comparable stability over 52 weeks at about 5 °C.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	°C	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		

15. Further evidence of the superior stability of the citrate buffer-based formulations disclosed in the '159 application can be found in exemplary formulations H1 and H7-H13 presented below in Table 1, which all contain a mixture of citric acid and sodium citrate.

16. Formulations H1 and H7-H13 were prepared according to the compositions in Table 1 and titrated if needed to the target pH with 5N hydrochloric acid or 5N sodium hydroxide. Formulations H1 and H7-H9 were placed into HDPE containers and sealed with screw caps and induction sealing and stored at 5 °C. Formulations H10-H13 were placed into glass containers, sealed with Teflon lined screw caps and stored at 60 °C. The formulations were sampled at various

times during storage. Samples were analyzed by HPLC for enalapril maleate and enalapril related substances. The results of the analyses are presented in Table 2 and Table 3.

17. The enalapril maleate assay results in Table 2 show that formulations H1 and H7-H9 retain greater than 98% of the initial enalapril maleate content and have less than 2% of total impurity after 52 weeks at 5 °C. Formulations H1 and H7-H9 demonstrated excellent stability. Further, by comparing the amounts of the two primary degradants (i.e., Diketopiperazine and Enalaprilat) in Table 2 and Table E-2, it can be expected that formulations E1-E6 have comparable stability to formulations H1 and H7-H9.

18. In Table 3, the stability of formulations prepared with a mixture of citric acid and sodium citrate as a buffer at two different concentrations and pH values were compared under an accelerated condition at 60 °C. The results in Table 3 show that a citrate buffer concentration of about 10 mM or 20 mM, at least when adjusted to a pH value of about 3-4, are suitable to be used in formulations of the '159 application and yield similar stability.

Table 1

Compositions (mg/mL) for Stability Testing								
Ingredients	H1 Citrate	H7 Citrate	H8 Citrate	H9 Citrate	H10 Citrate	H11 Citrate	H12 Citrate	H13 Citrate
Citric acid, anhydrous	1.82	1.92	1.92	1.92	1.92	1.92	3.84	3.84
Sodium citrate, dihydrate	0.15	-	-	-				
Citrate concentration (mM)	10	10	10	10	10	10	20	20
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose NF	0.70	0.70	0.70	0.70				
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	qs	qs	qs	qs	qs	qs	qs	qs
pH	3.3	3.3	4.0	4.5	3	4	3	4

Table 2

Assay and Total Degradant Content After Storage						
	Storage		Formulation			
	°C	Weeks	H1	H7	H8	H9
Enalapril Maleate (% initial)	5	0	100.0	100.0	100.0	100.0
		2	100.1	100.7	100.4	100.3
		4	100.2	99.8	100.0	99.6
		8	100.0	99.6	100.9	100.7

		24	99.8	100.4	100.1	99.8
		28	99.8	99.7	-	-
		36	-	-	99.9	99.4
		52	99.9	99.8	99.5	99.2
Diketopiperazine (% w/w of enalapril maleate)	5	0	<0.05	<0.05	<0.05	<0.05
		2	<0.05	<0.05	<0.05	<0.05
		4	<0.05	<0.05	<0.05	<0.05
		8	<0.05	<0.05	<0.05	<0.05
		24	0.06	0.07	<0.05	<0.05
		28	0.09	0.10	-	-
		36	-	-	0.06	<0.05
		52	0.14	0.12	0.07	<0.05
Enalaprilat (% w/w of enalapril maleate)	5	0	<0.05	<0.05	0.09	0.10
		2	0.06	0.07	0.13	0.16
		4	0.08	0.08	0.17	0.24
		8	0.15	0.14	0.27	0.37
		24	0.19	0.20	0.41	0.58
		28	0.35	0.36	-	-
		36	-	-	0.85	1.17
		52	0.53	0.52	1.10	1.49
Total Impurities (% w/w of enalapril maleate)	5	0	<0.05	<0.05	0.09	0.10
		2	0.07	0.07	0.14	0.16
		4	0.09	0.10	0.20	0.26
		8	0.18	0.18	0.31	0.41
		24	0.25	0.27	0.43	0.60
		28	0.44	0.46	-	-
		36	-	-	0.91	1.20
		52	0.68	0.65	1.18	1.53

Table 3
Assay Results After Storage of Formulations at 60 °C

Buffer	mM	Enalapril Maleate, pH 3 (% initial)				Enalapril Maleate, pH 4 (% initial)			
		0 Days	2 Days	4 Days	7 Days	0 Days	2 Days	4 Days	7 Days
Citrate	10	100.0	97.1	97.2	95.5	100.0	97.2	96.6	94.6
	20	100.0	97.1	96.8	95.2	100.0	96.8	96.4	94.4

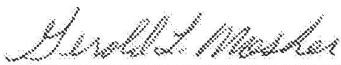
19. As presented above, Table E-2 and Tables 1-3 show that formulations of the '159 application can be prepared using a mixture of citric acid and sodium citrate, and the amount of the total citrate can vary, at least between about 5 mM and about 20 mM. All the formulations in Table E-2 and Tables 1-3 demonstrated superior stability, e.g., retaining greater than about 98% of the

initial enalapril maleate content and having less than about 2% w/w total impurity after 52 weeks at 5 °C.

20. Further, although formulations exemplified in the '159 application and in Tables 1-3 have a total citrate amount of about 5 mM, 10 mM or 20 mM, I would expect that similar formulations having a total citrate amount between about 5 mM and about 20 mM to have similar, superior stability as the exemplified formulations.

21. I declare that all statements made herein are true to the best of my knowledge, or if made upon information and belief, are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted on this 5th day of May, 2020



Gerold L. Mosher, Ph.D.

Attorney Docket No. 43060-707.305

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 1032
Serial No.: 16/242,898	Examiner: SPRINGER, Stephanie K
Filed: January 8, 2019	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on May 14, 2020, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u>/Paula Derby/</u></p>

Mail Stop Amendment

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132I, **Gerold Mosher**, state and declare as follows:

1. I am currently employed at Azurity Pharmaceuticals, Inc., a company formed in May 2019 by the acquisition of Silvergate Pharmaceuticals, Inc. by CutisPharma, Inc.

2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.

3. I have been employed at Silvergate Pharmaceuticals and now Azurity Pharmaceuticals since 2013, and my current position is Vice President of Product Development. As part of my job duties, I develop oral formulations for pediatric use. I have a small laboratory where I



develop, characterize and move formulations through the steps required for FDA approval and eventual sale.

4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also been employed by small startup companies to develop new solubilizing technology for oral, injectable, and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for about 40 years, and have extensive experience in developing pharmaceutical formulations. My *Curriculum Vitae* is attached as Exhibit A.

6. I am familiar with the subject matter claimed in U.S. Pat. App. Ser. No. 16/242,898 ("the '898 application"), and I am a named inventor on this application. Silvergate Pharmaceuticals, Inc. is the assignee of all rights in the invention of the pending '898 application.

7. I am aware of the Final Office Action mailed in this matter on November 19, 2019. I am also aware that the pending claims stand rejected as allegedly being obvious under 35 U.S.C. 103 over Nahata et al., "Stability of enalapril maleate in three extemporaneously prepared oral liquids," Am. J. Health-Syst. Pharm., 1998, vol. 55, pages 1155-1157 ("Nahata") in view of Sosnowska et al., "Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared From Commercially Available Tablets," Acta Poloniae Pharmaceutica - Drug Research, 2009, vol. 66, no. 3, pages 321-326 ("Sosnowska") in view of Boukarim et al., "Preservatives in Liquid Pharmaceutical Preparations", J. Appl. Res., 2009, vol. 9, no. 1&2, pages 14-17 ("Boukarim"). I have reviewed these cited references in the Final Office Action.

8. I am submitting this declaration to address the comments made in the Office Action.

9. The '898 application relates to enalapril oral liquid formulations that are stable at about 5 ± 3 °C for at least 12 months. The development of this described enalapril formulation was oriented on preparing a safe, stable, uniform oral liquid with minimal degradation and having an acceptable taste for pediatric patients.

10. Traditionally, approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in “Nahata” and subsequently administering the suspension to the patient, or (3) reconstituting a powder in a liquid carrier. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty swallowing solid oral dosage forms. For the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination.

11. As compared to these currently available methods, the enalapril oral liquid formulation claimed in the '898 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

12. The oral enalapril liquid formulations of the '898 application have superior stability—they are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

13. Evidence of the superior stability of the formulations disclosed in the '898 application can be found in exemplary formulations H1 to H9. Formulations H1 to H9 were prepared according to the compositions in Table 1 and titrated if needed to the target pH with 5N hydrochloric acid or 5N sodium hydroxide. The formulations were placed into HDPE containers and sealed with screw caps and induction sealing. The formulations were stored at 5 °C and 25 °C and sampled at various times. Samples were analyzed by HPLC for enalapril maleate and enalapril related substances. The results of the analyses are presented in Table 2.

14. As shown in Table 1 below, formulations H1- H9 were prepared with a variety of buffers, including sodium citrate, citric acid, phosphate, citrate/phosphate, acetate, glycine, and tartrate. Formulations H1 and H7-H9 contain citrate-based buffers. Specifically, formulation H1 was prepared with citric acid and sodium citrate, and formulations H7-H9 were prepared with citric acid only (no sodium citrate) with the pH being adjusted with HCl or NaOH. Formulations H2-H6 were prepared with phosphate, citrate/phosphate, acetate, glycine, and tartrate buffer, respectively. The pH values of formulations H1 to H9 vary from about 3.3 to about 4.5. The initial pH values of formulations H1 to H7 are about 3.3, and the initial pH values of formulations H8 and H9 are about 4.0 and 4.5, respectively.

15. The enalapril maleate assay results in Table 2 show that all the formulations have greater than 98% of the initial enalapril maleate content remaining after 52 weeks at 5 °C. The total impurity content is also less than 2% for the same period showing comparable stability between the formulations, irrespective of the type of buffers used.

Table 1

Compositions (mg/mL) for Stability Testing at 5 °C and 25 °C									
	H1	H2	H3	H4	H5	H6	H7	H8	H9
Ingredients	Citrate	Phosphate	Citrate/ Phosphate	Acetate	Glycine	Tartrate	Citrate	Citrate	Citrate
Acetic acid, glacial	-	-	-	0.58	-	-	-	-	-
Sodium Acetate	-	-	-	0.04	-	-	-	-	-
Citric acid, anhydrous	1.82	-	1.07	-	-	-	1.92	1.92	1.92
Sodium citrate, dihydrate	0.15	-	-	-	-	-	-	-	-
Glycine	-	-	-	-	0.75	-	-	-	-
Sodium dihydrogen phosphate, anhydrous	-	1.2	-	-	-	-	-	-	-
Disodium hydrogen	-	-	0.63	-	-	-	-	-	-

phosphate, anhydrous

L-(+)-tartaric acid	-	-	-	-	-	0.75	-	-	-
Sodium tartrate dibasic, dihydrate	-	-	-	-	-	1.15	-	-	-
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose NF	0.70	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
pH	3.3	3.3	3.3	3.3	3.3	3.3	3.3	4.0	4.5

Table 2

Assay and Total Degradant Content After Storage											
	Storage		Formulation								
	°C	Weeks	H1	H2	H3	H4	H5	H6	H7	H8	H9
Enalapril Maleate (% initial)	5	0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
		2	100.1	100.1	99.7	100.0	99.5	98.2	100.7	100.4	100.3
		4	100.2	100.3	99.6	100.4	100.0	98.9	99.8	100.0	99.6
		8	100.0	100.0	99.7	100.0	99.5	98.5	99.6	100.9	100.7
		24	99.8	100.0	99.6	100.2	99.4	98.6	100.4	100.1	99.8
		28	99.8	99.9	99.6	100.1	99.3	98.4	99.7	-	-
		36	-	-	-	-	-	-	-	99.9	99.4
		52	99.9	99.9	99.7	99.7	98.9	98.1	99.8	99.5	99.2
	25	0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
		2	100.1	99.2	99.7	100.0	99.5	98.4	99.8	99.9	99.5
		4	99.7	99.1	99.4	99.9	99.4	98.5	99.1	99.0	98.1
		8	98.8	98.0	98.5	99.0	98.3	97.4	98.3	99.3	97.7
		24	98.0	97.2	97.7	98.4	98.1	96.9	98.4	97.5	95.3
		28	95.8	95.1	95.5	96.5	96.1	94.7	95.6	-	-
		36	-	-	-	-	-	-	-	93.7	89.4
		52	93.9	93.3	93.5	94.3	93.9	92.4	93.6	91.7	86.0
Total Impurities (% w/w of enalapril maleate)	5	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.09	0.10
		2	0.07	0.07	0.07	0.06	0.06	0.06	0.07	0.14	0.16
		4	0.09	0.11	0.10	0.11	0.11	0.12	0.10	0.20	0.26
		8	0.18	0.20	0.18	0.16	0.16	0.18	0.18	0.31	0.41
		24	0.25	0.29	0.26	0.24	0.22	0.25	0.27	0.43	0.60
		28	0.44	0.47	0.47	0.42	0.41	0.44	0.46	-	-
		36	-	-	-	-	-	-	-	0.91	1.20
		52	0.68	0.71	0.71	0.64	0.66	0.68	0.65	1.18	1.53
	25	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.09	0.10
		2	0.46	0.47	0.47	0.39	0.39	0.41	0.51	0.63	0.95
		4	0.86	0.91	0.89	0.83	0.81	0.88	0.89	1.16	1.84
		8	1.71	1.79	1.76	1.53	1.51	1.64	1.70	2.21	3.49
		24	2.52	2.65	2.60	2.24	2.21	2.40	2.49	3.28	5.27
		28	4.91	5.18	5.08	4.49	4.43	4.81	4.94	-	-

36	-	-	-	-	-	-	-	7.32	11.60
52	7.22	7.64	7.45	6.67	6.60	7.16	7.25	9.55	14.95

16. Further evidence of the superior stability of the formulations disclosed in the '898 application can be found in exemplary formulations in Table 3. Formulations in Table 3 were prepared using fumarate, tartrate, malate, aspartate, glycinate, lactate, formate, phthalate, acetate, succinate, gluconate, glutamate, citrate, phosphate, and citrate/phosphate buffers, respectively. Specifically, these formulations were prepared according to the compositions in Table 3 and titrated if needed to pH 3 and 4 with 5N hydrochloric acid or 5N sodium hydroxide. The formulations were placed into amber glass screw-capped vial with Teflon lined caps. The vials were capped, stored at 60 °C and sampled at various times over 7 days. Samples were analyzed by HPLC for enalapril. The results of the analyses are presented in Table 4.

17. The citrate and phosphate 10mM formulations were included in Table 3 as a control since citrate and phosphate buffers were included in the previous study in Tables 1 and 2 and demonstrated superior stability. The enalapril maleate assay results in Table 4 show that all the formulations have stability comparable to the citrate formulations at 60 °C.

Table 3

Compositions (mg/mL) for Stability Testing at 60 °C												
Formula	Fumarate		Tartrate		Malate		Aspartate		Glycinate		Lactate	
	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM
Fumaric acid	2.32	1.16	-	-	-	-	-	-	-	-	-	-
Tartaric acid	-	-	3.00	1.50	-	-	-	-	-	-	-	-
DL-Malic acid	-	-	-	-	2.68	1.34	-	-	-	-	-	-
L-Aspartic acid	-	-	-	-	-	-	2.66	1.33	-	-	-	-
Glycine	-	-	-	-	-	-	-	-	1.50	0.75	-	-
Lactic acid	-	-	-	-	-	-	-	-	-	-	180	90
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
5N HCl/5N NaOH to pH	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0
Formula	Formate		Phthalate		Acetate		Succinate		Gluconate		Glutamate	
	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM
Formic acid	0.92	0.46	-	-	-	-	-	-	-	-	-	-

Potassium hydrogen phthalate	-	-	4.08	2.04	-	-	-	-	-	-	-	-
Acetic acid, glacial	-	-	-	-	1.20	0.60	-	-	-	-	-	-
Succinic acid	-	-	-	-	-	-	2.36	1.18	-	-	-	-
Sodium gluconate	-	-	-	-	-	-	-	-	4.36	2.18	-	-
L-Glutamic acid	-	-	-	-	-	-	-	-	-	-	2.94	1.47
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
5N HCl/5N NaOH to pH	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0

Formula	Citrate		Phosphate		Citrate/Phosphate 10mM each
	20mM	10mM	20mM	10mM	
Citric acid, anhydrous	3.84	1.92	-	-	1.92
Phosphoric acid	-	-	196	98	98
Sodium benzoate	1.00	1.00	1.00	1.00	1.00
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00
Purified water	Qs	Qs	Qs	Qs	Qs
5N HCl/5N NaOH to pH	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0

TABLE 4

Assay Results After Storage of Formulations at 60 °C

Buffer	mM	Enalapril Maleate, pH 3 (% initial)				Enalapril Maleate, pH 4 (% initial)			
		0 Days	2 Days	4 Days	7 Days	0 Days	2 Days	4 Days	7 Days
Citrate	10	100.0	97.1	97.2	95.5	100.0	97.2	96.6	94.6
	20	100.0	97.1	96.8	95.2	100.0	96.8	96.4	94.4
Phosphate	10	100.0	97.1	97.1	95.3	100.0	96.3	96.2	94.5
	20	100.0	97.1	96.7	95.2	100.0	96.3	96.0	94.2
Citrate/Phosphate	20	100.0	96.8	97.3	95.2	100.0	96.8	96.2	94.9
Tartrate	10	100.0	97.4	97.6	95.9	100.0	96.9	97.0	95.2
	20	100.0	97.2	97.6	95.6	100.0	97.1	96.4	94.0
Glycinate	10	100.0	98.7	96.4	95.4	100.0	96.8	96.6	95.3
	20	100.0	98.3	96.9	95.7	100.0	96.7	97.3	96.0
Acetate	10	100.0	97.5	97.4	95.1	100.0	96.7	96.8	95.3
	20	100.0	97.4	98.2	95.2	100.0	97.1	96.8	94.9
Malate	10	100.0	97.2	97.1	96.0	100.0	97.0	96.8	95.2
	20	100.0	97.2	97.1	95.9	100.0	96.7	96.5	95.0
Fumarate	10	100.0	96.6	96.8	95.2	100.0	95.9	96.1	94.4
	20	100.0	96.6	96.6	94.7	100.0	95.8	95.8	93.6
Succinate	10	100.0	98.1	96.2	95.3	100.0	96.6	96.8	94.5

	20	100.0	96.9	97.3	95.1	100.0	96.2	96.9	94.6
Aspartate	10	100.0	97.3	97.1	96.1	100.0	96.5	98.1	96.4
	20	100.0	97.0	97.4	95.8	100.0	96.6	97.0	95.3
Formate	10	100.0	97.0	97.1	95.6	100.0	96.6	97.1	93.8
	20	100.0	96.9	96.5	96.3	100.0	96.1	98.1	93.3
Gluconate	10	100.0	97.2	97.9	95.2	100.0	96.3	96.2	93.4
	20	100.0	97.0	98.9	94.2	100.0	96.2	95.8	94.2
Glutamate	10	100.0	97.2	96.9	95.9	100.0	96.9	96.4	95.3
	20	100.0	97.3	97.1	95.2	100.0	96.7	97.5	93.7
Lactate	10	100.0	97.3	97.1	96.4	100.0	96.5	98.3	95.3
	20	100.0	97.3	97.2	97.2	100.0	96.9	96.3	95.2
Phthalate	10	100.0	97.3	96.9	95.8	100.0	96.2	96.2	94.7
	20	100.0	97.0	96.8	95.5	100.0	96.2	97.8	93.3

18. As presented above, Tables 1-4 show that the formulations of the '898 application can be prepared using a variety of buffers (e.g., citrate, phosphate, citrate/phosphate, acetate, glycinate, fumarate, tartrate, malate, aspartate, lactate, formate, phthalate, acetate, succinate, gluconate, and glutamate buffers) and the pH values of the formulations can vary, e.g., at least from about 3 to about 4.5. All the formulations in Tables 1 and 3 demonstrated superior stability—retaining greater than 98% of the initial enalapril maleate content and having less than 2% w/w total impurity after 52 weeks at 5 °C, or having comparable stability when tested under an accelerated condition of 60 °C.

19. In my review of the references cited in the Office Action, none of the references describe this stability of at least 12 months at 5±3 °C or any means of achieving this stability for enalapril formulations.

20. I have reviewed Nahata which describes the extemporaneous preparation of oral liquid enalapril formulations by crushing enalapril tablets with a mortar and pestle and suspending the resulting ground tablets in water, citrate buffer, or Ora-Plus/Ora-Sweet. On stability, Nahata states that the “compounded oral liquids [were] stable for 91 days at 4 and 25 °C” defining stable as “concentration after storage was ≥90% of the initial concentration. Table 1 of Nahata shows that the enalapril extemporaneous formulations exhibited about 5% loss of enalapril after about 56 days at 4 °C and about 5% loss of enalapril after about 91 days at 25 °C.

21. I have reviewed Sosnowska, which similarly describes extemporaneous enalapril suspensions. The suspensions disclosed in Sosnowska were obtained by grinding tablets and suspending the resultant powder in a hydroxyethylcellulose solution or in a mixture that contains raspberry syrup and hydroxyethylcellulose solution. Based on the 30-day stability data shown in Table 1 of Sosnowska, these extemporaneous formulations have comparable stabilities to the formulations of Nahata, which is retaining about 98% of initial enalapril concentration after stored at refrigerated condition for 30 days. As noted in Sosnowska, “in the absence of microbiological data, the shelf-life given to extemporaneous products containing preservatives is usually 30 days.” Page 325 of Sosnowska.

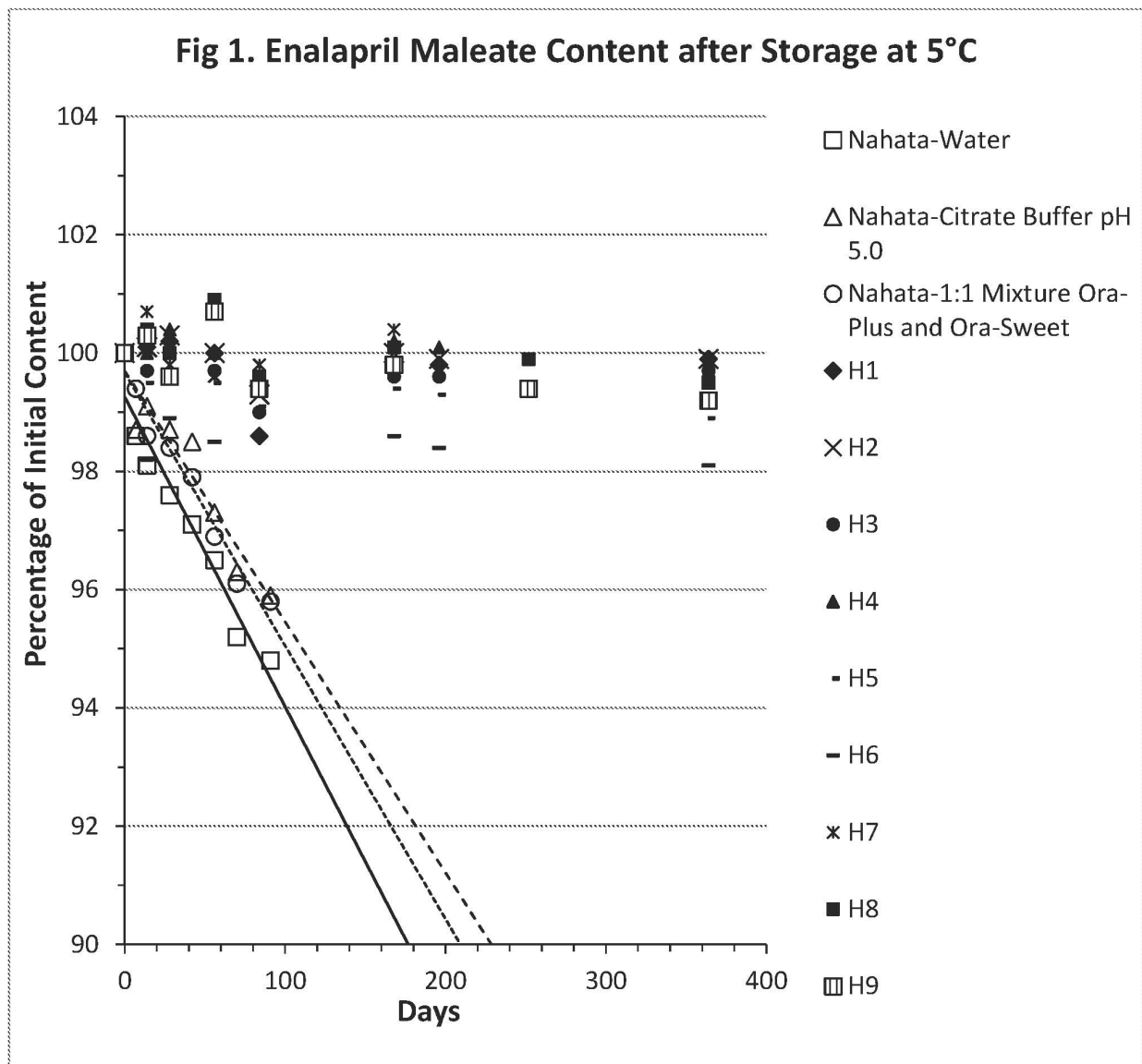
22. I have also reviewed Boukarim, which does not provide the stabilities of liquid enalapril formulations.

23. To compare the stability of the enalapril oral liquid formulations of the instant application with the extemporaneous preparations, such as those described in Nahata, the enalapril content of the Nahata formulations and that of formulations H1-H9 (stored at 5 °C) are provided in Table 5.

Table 5: Enalapril content in formulations after storage at 5 °C

Days	Nahata			Formulations of Instant Application								
	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	H1	H2	H3	H4	H5	H6	H7	H8	H9
0	100	100	100	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
7	98.6	98.7	99.4									
14	98.1	99.1	98.6	100.1	100.1	99.7	100.0	99.5	98.2	100.7	100.4	100.3
28	97.6	98.7	98.4	100.2	100.3	99.6	100.4	100.0	98.9	99.8	100.0	99.6
42	97.1	98.5	97.9									
56	96.5	97.3	96.9	100.0	100.0	99.7	100.0	99.5	98.5	99.6	100.9	100.7
70	95.2	96.3	96.1									
84				98.6	99.3	99.0	99.5	99.1	99.4	99.8	99.6	99.4
91	94.8	95.9	95.8									
168				99.8	100.0	99.6	100.2	99.4	98.6	100.4	100.1	99.8
196				99.8	99.9	99.6	100.1	99.3	98.4	99.7		
252											99.9	99.4
364				99.9	99.9	99.7	99.7	98.9	98.1	99.8	99.5	99.2

24. To further describe the contrast in stability, the enalapril concentrations published by Nahata, and the concentrations from H1-H9 are plotted graphically in Figure 1 with linear regression of the data for extrapolation.




25. Table 5 and Figure 1 show that formulations H1 to H9 exhibit excellent stability for at least 12 months (52 weeks) at 5 °C with essentially no or little loss of enalapril content, in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at about 5 °C for more

than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.

26. The enalapril content and total impurity data submitted in Tables 1-5 and Figure 1 show that the formulations of the present application are significantly more stable than the extemporaneously prepared formulations. Further, as shown by the stability of formulations H1-H9 and formulations of Table 3, a variety of buffers, which are capable of maintaining the pH values of the formulations at about or below 4.5, can be used in the formulations of the present application.

27. I declare that all statements made herein are true to the best of my knowledge, or if made upon information and belief, are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted on this 14th day of May, 2020



Gerold L. Mosher, Ph.D.

EXHIBIT 1



US008568747B1

(12) United States Patent
Rajewski et al.**(10) Patent No.: US 8,568,747 B1**
(45) Date of Patent: Oct. 29, 2013**(54) ENALAPRIL COMPOSITIONS****FOREIGN PATENT DOCUMENTS****(71)** Applicants: **University of Kansas**, Lawrence, KS (US); **Silvergate Pharmaceuticals**, Dublin, OH (US)WO WO-01/45667 6/2001
WO WO-2011/031462 3/2011
WO WO-2012/085249 6/2012
WO WO-2012/085249 * 6/2012 A61K 9/20**OTHER PUBLICATIONS****(72)** Inventors: **Lian G. Rajewski**, Lawrence, KS (US); **Roger A. Rajewski**, Lawrence, KS (US); **John L. Haslam**, Lawrence, KS (US); **Kathleen Heppert**, Lawrence, KS (US); **Michael C. Beckloff**, Leawood, KS (US); **Frank Seagrave**, Dublin, OH (US); **Robert Mauro**, Miller Place, NY (US); **Peter Colabuono**, Las Vegas, NV (US)Sosnowska et al. IDS dated Nov. 7, 2012.*
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Wang et al., "Eudragit E Accelerated the Diketoperazine Formation of Enalapril Maleate Determined by Thermal FTIR Microspectroscopic Technique," Pharmaceutical Research, vol. 21, No. 11, Nov. 2004.**(73)** Assignees: **Silvergate Pharmaceuticals, Inc.**, Dublin, OH (US); **University of Kansas**, Lawrence, KS (US)**(*)** Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.**(21)** Appl. No.: **13/670,355****(22)** Filed: **Nov. 6, 2012****Related U.S. Application Data****(60)** Provisional application No. 61/710,489, filed on Oct. 5, 2012.**(51)** **Int. Cl.**
A61K 31/41 (2006.01)**(52)** **U.S. Cl.**
USPC **424/400**; 514/224; 514/381**(58)** **Field of Classification Search**
None
See application file for complete search history.**(56)** **References Cited****U.S. PATENT DOCUMENTS**4,374,829 A 2/1983 Harris et al.
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(Continued)

Primary Examiner — Janet Epps-Smith*Assistant Examiner* — Yanzhi Zhang**(74)** *Attorney, Agent, or Firm* — Wilson, Sonsini, Goodrich & Rosati**(57)** **ABSTRACT**

Provided herein are stable enalapril powder compositions for oral liquid formulation. Also provided herein are methods of using enalapril oral liquid formulations for the treatment of certain diseases including hypertension, heart failure and asymptomatic left ventricular dysfunction.

6 Claims, 3 Drawing Sheets

US 8,568,747 B1

Page 2

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U.S. Patent

Oct. 29, 2013

Sheet 1 of 3

US 8,568,747 B1

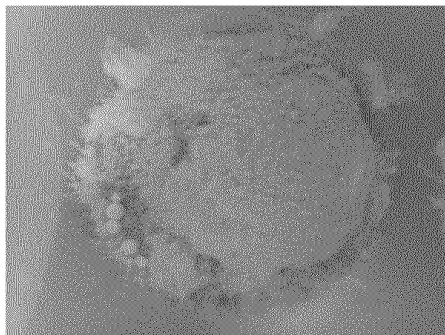


FIGURE 1

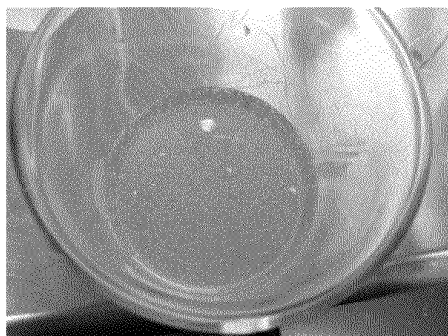


FIGURE 2A



FIGURE 2B



FIGURE 2C

U.S. Patent

Oct. 29, 2013

Sheet 2 of 3

US 8,568,747 B1

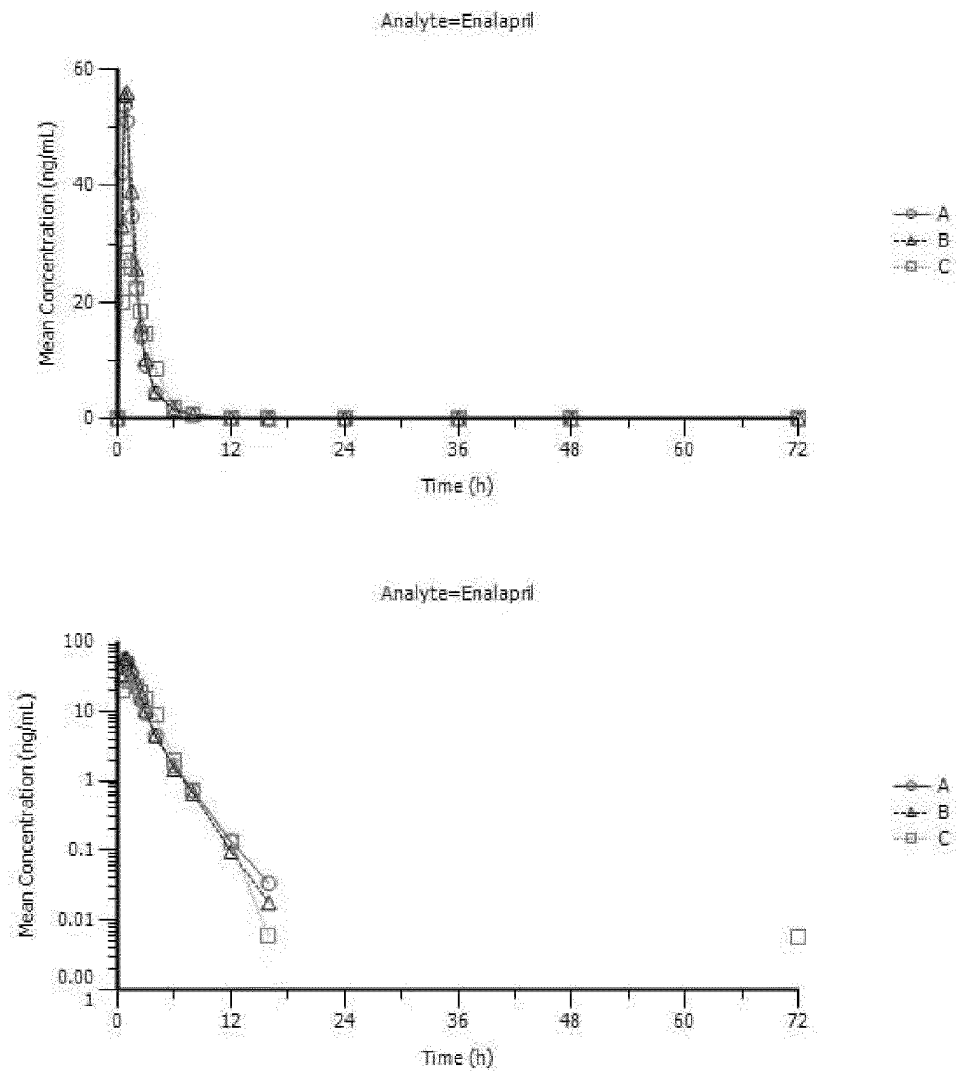


FIGURE 3

U.S. Patent

Oct. 29, 2013

Sheet 3 of 3

US 8,568,747 B1

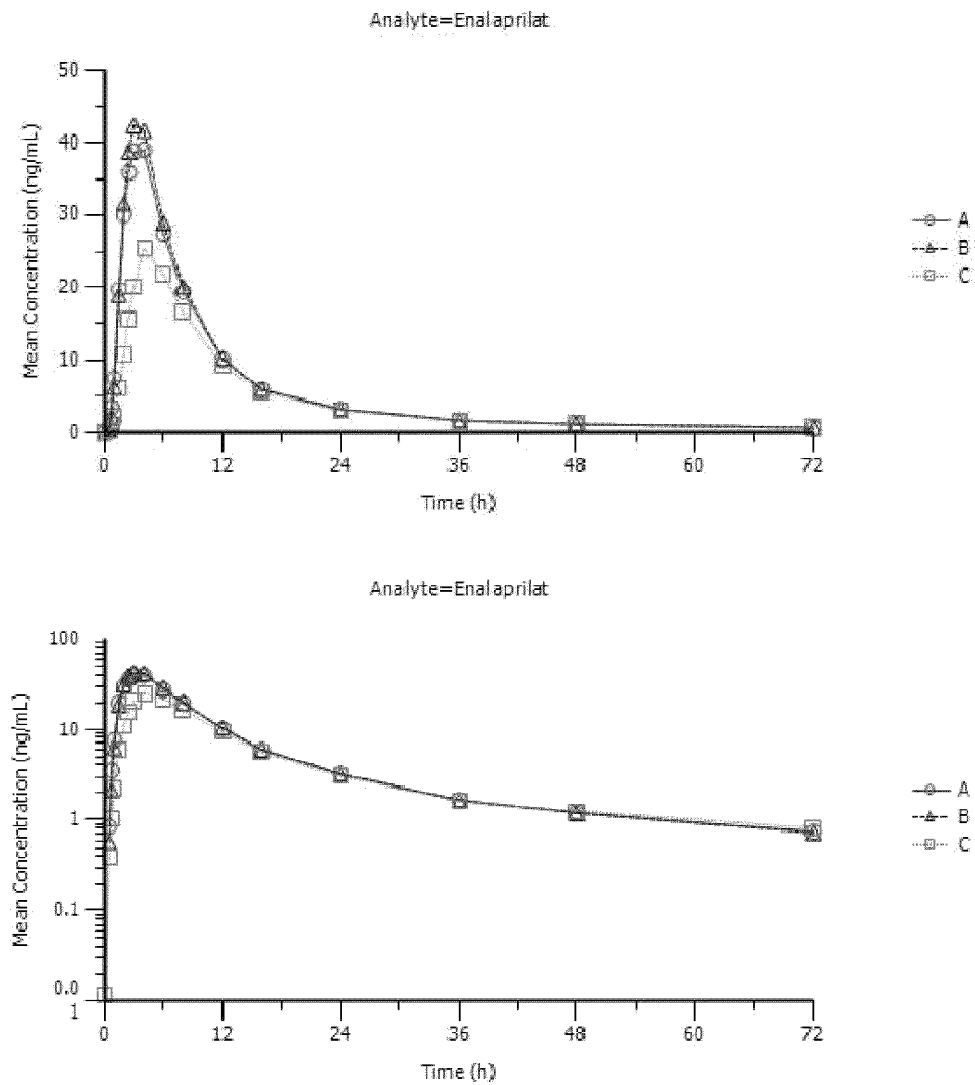


FIGURE 4

US 8,568,747 B1

1

ENALAPRIL COMPOSITIONS

CROSS REFERENCE

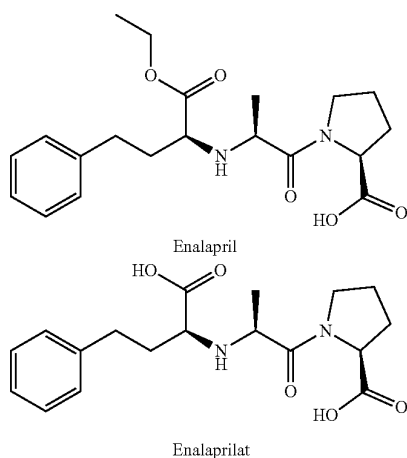
This application claims the benefit of U.S. Provisional Application Ser. No. 61/710,489, filed on Oct. 5, 2012, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and renin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotensin I to angiotensin II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat is as follows:



Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®). In addition to the treatment of hyper-

2

tension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril powder compositions for an oral liquid formulation. In one aspect, the powder comprises (a) about 1 to about 30% (w/w) enalapril or a pharmaceutically acceptable salt thereof, and (b) about 60 to about 99% (w/w) mannitol. In some embodiments, when the powder is reconstituted into an oral liquid, the liquid is homogenous and stable for at least 12 weeks at ambient or refrigerated conditions. In other embodiments, the powder is stable for at least six months at ambient, accelerated or refrigerated conditions. In certain instances, ambient conditions are $25 \pm 5^\circ \text{C}$. and $55 \pm 10\%$ relative humidity. In certain instances, refrigerated conditions are $5 \pm 3^\circ \text{C}$. In certain instances, accelerated conditions are about 40°C . or 60°C . and/or up to 80% relative humidity.

In another aspect, the powder comprises (a) about 1 to about 30% (w/w) enalapril or a pharmaceutically acceptable salt thereof, (b) about 60 to about 99% (w/w) mannitol, and (c) about 0.5 to about 2% (w/w) colloidal silicon dioxide. In some embodiments, when the powder is reconstituted into an oral liquid, the liquid is homogenous and stable for at least 12 weeks at ambient or refrigerated conditions. In other embodiments, the powder is stable for at least six months at ambient, accelerated or refrigerated conditions.

In certain embodiments, the enalapril is enalapril maleate. In certain embodiments, the powder is reconstituted in water for the oral liquid. In certain embodiments, the powder is reconstituted in a syrup for the oral liquid. In certain embodiments, the powder further comprises a pharmaceutically acceptable excipient. In certain instances, the pharmaceutically acceptable excipient is a sweetener, flavoring agent or preservative. In certain instances, the pharmaceutically acceptable excipient is a sweetener. In certain instances, the sweetener is a solid. In certain instances, the powder further comprises a solid (e.g., powder) sweetener. In certain instances, the sweetener is a liquid. In certain instances, the powder is reconstituted in a liquid sweetener (e.g., syrup). In certain embodiments, the enalapril or pharmaceutically acceptable salt thereof is about 12 to about 15% (w/w). In certain embodiments, the mannitol is about 80 to 85% (w/w). In certain embodiments, the silicon dioxide is about 1% (w/w). In certain embodiments, the enalapril or pharmaceutically acceptable salt thereof is about 14% (w/w), the mannitol is about 85% (w/w) and the silicon dioxide is about 1% (w/w). In certain embodiments, the powder comprises about 150 mg enalapril, about 890 mg mannitol and 10 mg colloidal silicon dioxide.

In another aspect, the powder comprises (a) about 1 to about 30% (w/w) enalapril or a pharmaceutically acceptable salt thereof, (b) about 60 to about 99% (w/w) mannitol, and (c) about 0.5 to about 2% (w/w) colloidal silicon dioxide, wherein, when the powder is reconstituted into an oral liquid, the liquid maintains no more than 5% total impurities for at least 12 weeks at ambient or refrigerated conditions. In another aspect, the powder comprises (a) about 1 to about 30% (w/w) enalapril or a pharmaceutically acceptable salt thereof, (b) about 60 to about 99% (w/w) mannitol, and (c) about 0.5 to about 2% (w/w) colloidal silicon dioxide, wherein, the powder maintains no more than 5% total impurities for at least six months at ambient, accelerated or refrigerated conditions.

US 8,568,747 B1

3

In certain embodiments, the liquid maintains no more than 2.5% total impurities for at least 12 weeks. In certain embodiments, the liquid maintains no more than 2.5% enalaprilat for at least 12 weeks. In certain embodiments, the liquid maintains no more than 2.5% diketopiperazine for at least 12 weeks. In certain embodiments, the powder maintains no more than 2.5% total impurities for at least six months. In certain embodiments, the powder maintains no more than 1% enalaprilat for at least six months. In certain embodiments, the powder maintains no more than 1% diketopiperazine for at least six months.

Also provided herein are enalapril oral liquid formulations. In one aspect, the liquid formulation comprises (a) about 0.5 to about 5 mg/mL enalapril or a pharmaceutically acceptable salt thereof, (b) about 3 to about 10 mg/mL mannitol, and (c) a sweetener; wherein, the liquid is homogenous and stable for at least 12 weeks at ambient or refrigerated conditions.

In another aspect, the liquid formulation comprises (a) about 0.5 to about 5 mg/mL enalapril or a pharmaceutically acceptable salt thereof, (b) about 3 to about 10 mg/mL mannitol, (c) about 0.03 to about 0.13 mg/mL colloidal silicon dioxide, and (d) a sweetener; wherein, the liquid is homogenous and stable for at least 12 weeks at ambient or refrigerated conditions.

In certain embodiments, the enalapril is enalapril maleate. In certain embodiments, the liquid formulation comprises about 1 mg/mL enalapril. In certain embodiments, the liquid formulation comprises about 5 mg/mL mannitol. In certain embodiments, the liquid formulation comprises about 6 mg/mL mannitol. In certain embodiments, the liquid formulation comprises about 0.06 mg/mL colloidal silicon dioxide. In certain embodiments, liquid formulation comprises about 1 mg/mL enalapril, about 6 mg/mL mannitol and about 0.06 mg/mL colloidal silicon dioxide.

In certain embodiments, the sweetener is sorbitol. In certain embodiments, the liquid formulation comprises an additional pharmaceutically acceptable excipient. In certain instances, the pharmaceutically acceptable excipient is a flavoring agent or preservative. In certain embodiments, the liquid formulation comprises water as the liquid vehicle. In certain embodiments, the liquid formulation comprises a syrup as the liquid vehicle.

In another aspect, the liquid formulation comprises (a) about 1 mg/mL enalapril or a pharmaceutically acceptable salt thereof, (b) about 6 mg/mL mannitol, (c) about 0.07 mg/mL colloidal silicon dioxide, and (d) a sweetener, wherein the liquid formulation maintains an 80-125% C_{max} of 58 ng/mL following oral administration at a 10 mg enalapril dosage for at least 12 weeks.

In some embodiments, when the liquid formulation is stored at up to 12 weeks at ambient or refrigerated conditions after reconstitution, the liquid formulation provides an 80-125% C_{max} of 58 ng/mL enalapril following oral administration at a 10 mg enalapril dosage. In some embodiments, when the liquid formulation is stored at up to 12 weeks at ambient or refrigerated conditions, the liquid formulation provides an 80-125% C_{max} of 41 ng/mL enalaprilat following oral administration at a 10 mg enalapril dosage.

In some embodiments, when the liquid formulation is stored at up to 12 weeks at ambient or refrigerated conditions after reconstitution, the liquid formulation provides an 80-125% AUC_{inf} of 102.6 h*ng/mL enalapril following oral administration at a 10 mg enalapril dosage. In some embodiments, when the liquid formulation is stored at up to 12 weeks at ambient or refrigerated conditions, the liquid formulation provides an 80-125% AUC_{inf} of 405.3 h*ng/mL enalaprilat following oral administration at a 10 mg enalapril dosage.

4

In some embodiments, when the liquid formulation is stored at up to 12 weeks at ambient or refrigerated conditions after reconstitution, the liquid formulation provides an 80-125% T_{max} of 0.87 h for enalapril following oral administration at a 10 mg enalapril dosage. In some embodiments, when the liquid formulation is stored at up to 12 weeks at ambient or refrigerated conditions, the liquid formulation provides an 80-125% T_{max} of 3.45 h for enalaprilat following oral administration at a 10 mg enalapril dosage.

Also provided herein are processes for preparing an enalapril oral liquid formulation. In one aspect, the process comprises the steps of (i) providing a uniform powder comprising about 10 to about 20% (w/w) enalapril or a pharmaceutically acceptable salt thereof, about 60 to about 90% (w/w) mannitol, and about 0.5 to about 1% (w/w) colloidal silicon dioxide in a bottle; (ii) adding an amount of sweetener in liquid syrup form; (iii) shaking the liquid formulation for at least 10 seconds; (iv) adding a second amount of sweetener in liquid syrup form; (v) shaking the liquid formulation for at least 10 seconds; and (vi) allowing the formulation in the bottle to stand for at least one hour to allow bubble dissipation.

Also provided herein are methods of treating hypertension or heart failure comprising administering to a patient in need thereof an oral liquid formulation reconstituted from an enalapril powder as described herein. In one embodiment, the patient is a child. In another embodiment, the patient is elderly.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1: Scaled-up enalapril powder composition A blended for 60 minutes showing formulation of balls and segregation.

FIG. 2: Reconstitution of various enalapril powder compositions: enalapril and mannitol (2A), neat enalapril (2B), and enalapril, mannitol and colloidal silicon dioxide (2C).

FIG. 3: Mean enalapril concentration-time profiles (linear, top; log, bottom) after administration of test formulation—fasted (Treatment A), reference product—fasted (Treatment B), and test formulation—fed (Treatment C).

FIG. 4: Mean enalaprilat concentration-time profiles (linear, top; log, bottom) after administration of test formulation—fasted (Treatment A), reference product—fasted (Treatment B), and test formulation—fed (Treatment C).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril powder compositions for oral liquid administration. Also provided herein are stable enalapril oral liquid compositions. These enalapril compositions described herein are useful for the treatment of hypertension, heart failure as well as ventricular dysfunction. The

US 8,568,747 B1

5

compositions are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, better absorption, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

For enalapril, the current solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming an enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

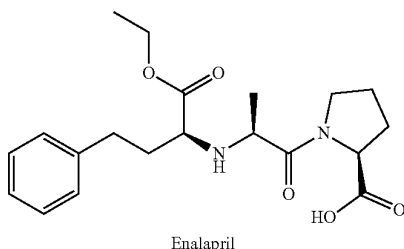
The present embodiments provide a safe and effective oral administration of enalapril for the treatment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid compositions as well as enalapril powder compositions for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the compositions described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

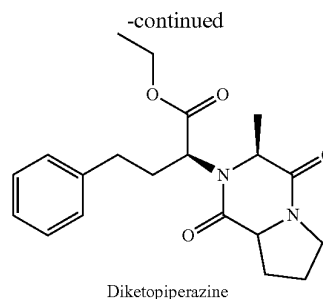
Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, complexes, thereof.

Enalapril Powder Compositions

In one aspect, enalapril powder compositions herein comprise enalapril and mannitol as a stabilizing agent. By itself, enalapril is temperature stable under dry or stable conditions. However, when mixed in a matrix such as in a tablet with additional excipients, enalapril is unstable and can degrade to an unwanted cyclized diketopiperazine (DKP).



6



It is contemplated that lactose in enalapril solid tablet formulations aid in preventing degradation to diketopiperazine and/or other related substances. However, surprisingly, as shown in Example 1, powder blends of lactose with enalapril showed the greatest degradation whereas enalapril/mannitol powder was most stable under accelerated conditions. This was also observed for the prepared solutions from the powder blends (Example 2).

In some embodiments, enalapril is present in about 1% w/w to about 30% w/w of the powder composition. In some embodiments, enalapril is present in about 2% w/w to about 25% w/w, about 5% w/w to about 20% w/w, about 7% w/w to about 18% w/w, about 10% w/w to about 16% w/w, or about 12% w/w to about 15% w/w of the powder composition. In other embodiments, enalapril is present in about 1% w/w, about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w or about 30% w/w of the powder composition. In certain embodiments, enalapril is present in about 1% w/w of the powder composition. In certain other embodiments, enalapril is present in about 2% w/w of the powder composition. In certain other embodiments, enalapril is present in about 10% w/w of the powder composition. In certain other embodiments, enalapril is present in about 14% w/w of the powder composition. In certain other embodiments, enalapril is present in about 15% w/w of the powder composition. In certain other embodiments, enalapril is present in about 20% w/w of the powder composition.

In some embodiments, mannitol is present in about 60% w/w to about 99% w/w of the powder composition. In some embodiments, mannitol is present in about 65% w/w to about 95% w/w, about 70% w/w to about 90% w/w or about 75% w/w to about 85% w/w of the powder composition. In other embodiments, mannitol is present in about 99% w/w, about 98% w/w, about 97% w/w, about 96% w/w, about 95% w/w, about 94% w/w, about 93% w/w, about 92% w/w, about 91% w/w, about 90% w/w, about 89% w/w, about 88% w/w, about 87% w/w, about 86% w/w, about 85% w/w, about 84% w/w, about 83% w/w, about 82% w/w, about 81% w/w, about 80% w/w, about 79% w/w, about 78% w/w, about 77% w/w, about 76% w/w, about 75% w/w, about 74% w/w, about 73% w/w, about 72% w/w, about 71% w/w, about 70% w/w, about 69% w/w, about 68% w/w, about 67% w/w, about 66% w/w, about 65% w/w, about 64% w/w, about 63% w/w, about 62% w/w, about 61% w/w or about 60% w/w of the powder composition. In certain embodiments, mannitol is present in about 1% w/w of the powder composition. In certain other embodiments, mannitol is present in about 99% w/w of the powder

US 8,568,747 B1

7

composition. In certain other embodiments, mannitol is present in about 90% w/w of the powder composition. In certain other embodiments, mannitol is present in about 85% w/w of the powder composition. In certain other embodiments, mannitol is present in about 80% w/w of the powder composition. In certain other embodiments, mannitol is present in about 70% w/w of the powder composition. In certain other embodiments, mannitol is present in about 60% w/w of the powder composition.

In further embodiments, the enalapril powder compositions herein comprises additional excipients including, but not limited to, buffering agents, glidants, preservatives, sweeteners, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Buffering agents maintain the pH when enalapril powder compositions are reconstituted into a liquid form. Non-limiting examples of buffering agents include, but are not limited to, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, a mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the enalapril powder compositions described herein comprise a buffering agent.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder compositions described herein comprise a glidant. In certain instances, enalapril powder compositions described herein comprise colloidal silicon dioxide.

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (methyl-, ethyl-, butyl-), benzoic acid, potassium sorbate, vanillin, and the like. In some embodiments, the enalapril powder compositions described herein comprise a preservative.

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, the enalapril powder compositions described herein comprise a sweetener. Solid, powder sweeteners, in some embodiments, are blended with the enalapril powder compositions described herein. In other embodi-

8

ments, sweeteners in liquid form referred to as syrups are used to solvate or dissolve the enalapril powder compositions described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, mannitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003—propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005—maltodextrin, sorbitol, and fructose combination and Product Code 918.010—water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), Maltisweet™ (maltitol solution, Ingredion) and Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn syrup, Ingredion) and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing. In certain instances, an above-described syrup is used to solvate or dissolve the enalapril powder compositions described herein. In further instances, Ora-Sweet® sugar-free flavored syrup is used to solvate or dissolve the enalapril powder compositions described herein.

In some embodiments, the sweetener imparts a sweet sensation equivalent to an about 50% to about 95% w/v sucrose in water. In some embodiments, the sweetener imparts a sweet sensation equivalent to an about 50% w/v, about 55% w/v, about 60% w/v, about 65% w/v, about 70% w/v, about 75% w/v, about 85% w/v (e.g., simple syrup NF), about 90% w/v, or about 95% w/v sucrose in water. In some embodiments, the sweetener imparts a sweet sensation equivalent to an about 60% to about 80% w/v sorbitol in water. In some embodiments, the sweetener imparts a sweet sensation equivalent to an about 60% w/v, about 65% w/v, about 70% w/v, about 75% w/v or about 80% w/v sorbitol in water. In some embodiments, the sweetener imparts a sweet sensation equivalent to an about 64% w/v sorbitol in water.

In another embodiment, the enalapril powder compositions comprise a flavoring agent or flavorant to enhance the taste or aroma of the composition in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the composition is

US 8,568,747 B1

9

intended primarily for pediatric use, is tutti-frutti or bubble-gum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum and vanilla. In some embodiments, the enalapril powder compositions described herein comprise a wild cherry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder compositions comprise a coloring agent for identity and/or aesthetic purposes of the resultant liquid form. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril compositions described herein. Exemplary thickeners include dextrin, cellulose derivatives (ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril powder compositions comprise a thickener.

Additional excipients are contemplated in the enalapril powder composition embodiments. These additional excipients are selected based on function and compatibility with the enalapril powder compositions described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In certain embodiments, an additional excipient is present in about 1% w/w to about 30% w/w of the enalapril powder composition. In certain embodiments, an additional excipient is present in about 2% w/w to about 25% w/w, about 5% w/w to about 20% w/w, about 7% w/w to about 15% w/w or about 10% w/w to about 12% w/w of the enalapril powder composition. In other embodiments, an additional excipient is present in about 1% w/w, about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w or about 30% w/w of the enalapril powder composition.

Preparation of Enalapril Powder Compositions

Preparation of enalapril powder compositions described herein includes any known pharmaceutical method. In one embodiment, the enalapril powder compositions described herein are prepared by a granulation method. In an exemplary granulation method, enalapril is dissolved in water or a solution (e.g., sodium bicarbonate) which is subsequently sprayed onto mannitol. The wetted material is then dried via heat (e.g., 40°-60° C. oven) or air-dried. The dried granulation is then passed through a 40-mesh screen, for example.

In another embodiment, the enalapril powder compositions described herein are prepared by a direct blend method. In one example, enalapril is blended with mannitol along with any other excipients in a dry mixer or blender. In certain instances, the powders are passed through a mesh screen prior

10

to and/or after mixing. The dry blend is facilitated by conventional large-scale mixing equipment such as rotating-shell mixers (e.g., drum-type, cubical shaped, double-cone and twin-shell blender), fixed-shell (ribbon) mixers, sigma-blade and planetary paddle mixers, vertical impeller mixers and motionless mixers. The mixing is performed to blend uniformity of the enalapril powder compositions described herein. In embodiments with additional excipients, mixing methods can include all components together or incorporate certain components together first with other components subsequently added.

In an additional embodiment, the enalapril powder compositions described herein additionally comprise colloidal silicon dioxide in scale-up preparation. Although colloidal silicon dioxide has been reported to decrease stability of enalapril, (Rezende et al., Stability and Compatibility Study on Enalapril Maleate using Thermoanalytical Techniques, *J. Thermal Anal. & Calorimetry*, 2008 (93) 881-886), the addition of colloidal silicon dioxide surprisingly aided in the uniformity of the blend and the bottle content as well as in preparation of the liquid form (see Example 4).

In some embodiments, colloidal silicon dioxide is present in about 0.1% w/w to about 2% w/w of the powder composition. In some embodiments, colloidal silicon dioxide is present in about 0.1% w/w to about 2% w/w, about 0.2% w/w to about 1.7% w/w, about 0.3% w/w to about 1.5%, about 0.4% w/w to about 1.2% or about 0.5 w/w to about 1.0% w/w of the powder composition. In other embodiments, colloidal silicon dioxide is present in about 0.1% w/w, about 0.2% w/w, about 0.3% w/w, about 0.4% w/w, about 0.5% w/w, about 0.6% w/w, about 0.7% w/w, about 0.8% w/w, about 0.9% w/w, about 1.0% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w or about 2.0% w/w of the powder composition. In certain embodiments, colloidal silicon dioxide is present in about 0.1% w/w of the powder composition. In certain other embodiments, colloidal silicon dioxide is present in about 0.5% w/w of the powder composition. In certain other embodiments, colloidal silicon dioxide is present in about 1.0% w/w of the powder composition. In certain other embodiments, colloidal silicon dioxide is present in about 1.2% w/w of the powder composition. In certain other embodiments, colloidal silicon dioxide is present in about 1.5% w/w of the powder composition. In certain other embodiments, colloidal silicon dioxide is present in about 1.7% w/w of the powder composition. In certain other embodiments, colloidal silicon dioxide is present in about 2.0% w/w of the powder composition.

Stability of Enalapril Powder Compositions

The enalapril powder compositions described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder compositions having about 95% enalapril and about 5% or less total impurities or substances at the end of a given storage period. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder compositions have about 5%, about 4%, about 3%, about 2.5%, about 2%, about 1.5%, about 1%, or about 0.5% total impurities or substances. In other embodiments, the stable enalapril powder compositions have about 5% total impurities or substances. In yet other embodiments, the stable enalapril powder compositions have about 4% total impurities or substances. In yet other embodiments, the stable enalapril powder compositions have about 3% total impurities or substances. In yet other embodiments, the stable enalapril powder compositions have about 2% total

US 8,568,747 B1

11

impurities or substances. In yet other embodiments, the stable enalapril powder compositions have about 1% total impurities or substances. In further embodiments, the stable enalapril powder compositions have about 95%, about 96%, about 97%, about 98% or about 99% enalapril at the end of a given storage period.

At refrigerated and ambient conditions, the enalapril powder compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. At accelerated conditions, the enalapril powder compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions include temperature and/or relative humidity (RH) that are above ambient levels (e.g. $25\pm 5^\circ\text{C}$.; $55\pm 10\%$ RH). In some instances, an accelerated condition is at about 30°C ., about 35°C ., about 40°C ., about 45°C ., about 50°C ., about 55°C . or about 60°C . In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40°C . or 60°C . at ambient humidity. In yet further instances, an accelerated condition is about 40°C . at $75\pm 5\%$ RH humidity. Ambient conditions include temperature and/or relative humidity (RH) that are at ambient levels (e.g. $25\pm 5^\circ\text{C}$.; $55\pm 10\%$ RH). In some instances, an ambient condition is at about 20°C ., about 21°C ., about 22°C ., about 23°C ., about 24°C ., about 25°C ., about 26°C ., about 27°C ., about 28°C ., about 29°C ., or about 30°C . In other instances, an ambient condition is about 45% RH, about 50% RH, about 55% RH, about 60% RH or about 65% RH. Refrigerated conditions include temperature and/or relative humidity (RH) in typical refrigeration units (e.g., $5\pm 3^\circ\text{C}$.). In some instances, a refrigerated condition is at about 2°C ., about 3°C ., about 4°C ., about 5°C ., about 6°C ., about 7°C . or about 8°C . In other instances, a refrigerated condition is at about 4°C .

Enalapril Oral Liquid Compositions

In another aspect, enalapril powder compositions described herein are useful for the preparation or reconstitution of an enalapril oral liquid. Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components of the enalapril powder compositions described herein are in a solution while other components are in a suspension. By way of illustrative example only, when an enalapril powder composition comprising enalapril, mannitol and an excipient such as colloidal silicon dioxide or a powdered cellulose is dissolved in water or other aqueous solvent, the enalapril and mannitol are in solution whereas the colloidal silicon dioxide or powdered cellulose would form a suspension in the aqueous environment. In some embodiments, the enalapril oral liquid compositions are solutions. In other embodiments, the enalapril oral liquid compositions are suspensions. In yet other embodiments, the enalapril oral liquid compositions are solution/suspensions.

Liquid vehicles suitable for the enalapril powder compositions described herein are selected for a particular oral liquid composition (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other

12

sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for an enalapril oral liquid. In other embodiments, a syrup is used for as a vehicle for an enalapril oral liquid. In yet other embodiments, a juice is used for as a vehicle for an enalapril oral liquid.

The enalapril liquids prepared from the powder compositions described herein, in some embodiments, are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. Such exemplary tests include visual inspection of the resultant liquid for air bubbles and/or undissolved solids which may cause variable dosing. Analytical HPLC testing can also determine drug concentration uniformity by examining aliquots of certain volume sections (e.g., 5 or 10 mL from the top, middle and bottom of a 150 mL bottle). The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril liquid.

Mixing methods encompass any type of mixing that results in a homogenous enalapril liquid composition. In some embodiments, a quantity of an enalapril powder composition is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of an enalapril powder composition (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder composition in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to an enalapril powder composition in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof; and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder composition in a container and mixing by shaking; the other one-half fractional volume of the liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2×10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, an enalapril liquid composition is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 min-

US 8,568,747 B1

13

utes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Oral Liquid Compositions

The enalapril oral liquid compositions described herein are stable in various storage conditions including refrigerated and ambient conditions. Stable as used herein refer to enalapril oral liquid compositions having at least about 90% enalapril and 5% or less total impurities or substances at the end of a given storage period. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid compositions have about 5%, about 4%, about 3%, about 2.5%, about 2%, about 1.5%, about 1%, or about 0.5% total impurities or substances. In other embodiments, the stable enalapril oral liquid compositions have about 5% total impurities or substances. In yet other embodiments, the stable enalapril oral liquid compositions have about 4% total impurities or substances. In yet other embodiments, the stable enalapril oral liquid compositions have about 3% total impurities or substances. In yet other embodiments, the stable enalapril oral liquid compositions have about 2% total impurities or substances. In yet other embodiments, the stable enalapril oral liquid compositions have about 1% total impurities or substances. In further embodiments, the stable enalapril oral liquid compositions have at least about 90%, at least about 91%, at least about 92%, at least about 93%, or at least about 94% enalapril at the end of a given storage period.

At refrigerated and ambient conditions, in some embodiments, the enalapril oral liquid compositions described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. In other embodiments, the enalapril oral liquid compositions described herein are stable at refrigerated and ambient conditions for at least 12 weeks. Ambient conditions include temperature and/or relative humidity (RH) that are at ambient levels (e.g. $25 \pm 5^\circ \text{C}$.; $55 \pm 10\% \text{RH}$). In some instances, an ambient condition is at about 20°C ., about 21°C ., about 22°C ., about 23°C ., about 24°C ., about 25°C ., about 26°C ., about 27°C ., about 28°C ., about 29°C ., or about 30°C . In other instances, an ambient condition is about 45% RH, about 50% RH, about 55% RH, about 60% RH or about 65% RH. Refrigerated conditions include temperature and/or relative humidity (RH) in typical refrigeration units (e.g., $5 \pm 3^\circ \text{C}$). In some instances, a refrigerated condition is at about 2°C ., about 3°C ., about 4°C ., about 5°C ., about 6°C ., about 7°C ., or about 8°C . In other instances, a refrigerated condition is at about 4°C .

In further embodiments, the stable enalapril oral liquid compositions described herein that are stored at ambient or refrigerated conditions for a give storage period after reconstitution provide similar, consistent or equivalent pharmacokinetic parameters as an enalapril oral liquid composition that is formulated prior to administration to a subject (i.e., freshly made). In other words, the enalapril oral liquid compositions described herein have stability after a storage period to provide similar, consistent or equivalent pharmacokinetic parameters as a freshly made enalapril oral liquid composition. For example, a 12 week stable enalapril oral liquid composition provides similar, consistent or equivalent pharmacokinetic parameters as an enalapril oral liquid composition made five minutes prior administration. Pharmacokinetic parameters include C_{max} , T_{max} , AUC_{last} , AUC_{inf} , $T_{1/2}$, C_{last} for enalapril and/or enalaprilat and exemplary values are obtained and described in Example 7. In some instances, the stable enalapril oral liquid compositions described herein

14

provide within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110% pharmacokinetic parameters of a freshly made enalapril oral liquid composition when the stable composition is stored at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks after reconstitution. In other instances, the stable enalapril oral liquid compositions described herein provide within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110% pharmacokinetic parameters of a freshly made enalapril oral liquid composition when the stable composition is stored for 12 weeks after reconstitution.

Kits and Articles of Manufacture

For the enalapril powder and liquid compositions described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid composition. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid composition described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid composition. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid compositions described herein to a subject. In some embodiments, the enalapril oral liquid compositions described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension or secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid compositions described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid compositions described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid compositions described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid compositions described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are

US 8,568,747 B1

15

120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid compositions described herein treat a subject having a blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid compositions described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid compositions described herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid compositions described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid compositions described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid compositions described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid compositions described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid compositions described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid compositions described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid compositions described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid compositions are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid compositions in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid compositions described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid composition that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., age, weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific

16

agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid compositions described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid compositions described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76 mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid compositions described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid compositions described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid compositions are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid compositions are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid compositions is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg. In a further embodiment, the daily dosage appropriate for the enalapril oral liquid compositions is about 0.08 mg/kg.

In other embodiments the enalapril oral liquid compositions are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid compositions administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or

US 8,568,747 B1

17

about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid compositions administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid compositions are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid compositions are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid composition is at a dosage described herein or at other dose levels and compositions determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid compositions described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid compositions are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the age of the patient, severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril compositions, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid compositions described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's age, state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril compositions, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid composition described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid composition continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid composition being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365

18

days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid compositions described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid composition is administered as a continuous dose, i.e., administered daily to a subject. In some other embodiments, enalapril oral liquid compositions described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the composition is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid composition is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid composition is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid composition is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid composition is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid composition is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid composition is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid composition is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid composition is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid composition is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid composition is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid composition is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid composition can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid composition is administered in the morning. In other embodiments, an enalapril oral liquid composition can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid composition can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid composition described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct

US 8,568,747 B1

19

conditions associated with the disease or condition or a side effect from the enalapril oral liquid composition in the therapy.

Additional agents for use in combination with an enalapril oral liquid composition described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phenolamine, phenoxybenzamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartin, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

“Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

“Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril composition, can include, but is not limited to, providing an enalapril composition into or onto the target tissue; providing an enalapril composition systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a composition may

20

be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms “patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is under the age of 12 years. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a composition of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symp-

US 8,568,747 B1

21

toms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example 1

Stability of Enalapril Formulated Powder

Enalapril Powder Formulation:

The stability of enalapril with lactose, sucrose or mannitol was assessed in various storage conditions. 2% w/w enalapril powder was formulated via granulation according to the following table.

Component	Amount in Bottle (mg)	Weight (% w/w solids)	Batch (g)
Enalapril Maleate	150	2.0	6,000
Stability Agent (Lactose, Sucrose or Mannitol)	7350	98.0	294.0
Sodium Bicarbonate	—	—	3,074
Water	—	—	25.00
Total Solids	7500	100.0	300.0

Enalapril Maleate was slowly dissolved in a 12% sodium bicarbonate solution. The stability agent (lactose, sucrose or mannitol) was mixed in a mixer at slow speed and the enalapril solution was slowly sprayed onto the stability agent over a period of about 20 minutes. The wetted material was spread onto a dish and placed in a 60° C. oven for at least 4 h. The dried granulation was passed through a 40-mesh screen.

Stability Studies:

The effect of the three stability agents, lactose, mannitol and sucrose on the stability of the granulated powder was evaluated. 7.5 g of powder was placed in 8 oz amber, graduated PET bottles and stored under refrigerated, 25° C./60% Relative Humidity (RH), 40° C./ambient and 60° C./ambient conditions. At various time points the powder in the bottle was analyzed for enalapril by HPLC/UV analysis. The following tables depict the stability of enalapril+stability agent powder in bottle in the various storage conditions.

22

2% w/w Enalapril/Lactose
Powder in Bottle Formulation

Time (Weeks)	Refrigerated	25° C./ 60% RH	40° C./ ambient	60° C./ ambient
0	101.54	101.54	101.54	101.54
1	100.27	100.59	98.61	94.74
2	100.37	100.60	98.82	94.51
3	101.10	99.58	98.45	93.44
4	99.03	98.53	96.94	92.66
8	100.23	99.63	98.89	90.56
12	102.20	99.53	100.02	89.76
26	101.28	95.83	97.89	75.57
52	101.50	91.90	93.70	N/A

2% w/w Enalapril/Mannitol
Powder in Bottle Formulation

Time (Weeks)	Refrigerated	25° C./ 60% RH	40° C./ ambient	60° C./ ambient
0	100.16	100.16	100.16	100.16
1	99.61	99.57	93.42	96.96
2	98.56	98.41	94.41	101.14
3	99.21	98.51	99.42	101.24
4	99.20	98.59	101.26	99.97
8	101.26	98.88	102.17	100.80
12	103.33	99.67	103.31	95.15
26	102.19	96.89	102.68	94.66
52	102.50	94.30	99.70	N/A

2% w/w Enalapril/Sucrose
Powder in Bottle Formulation

Time (Weeks)	Refrigerated	25° C./ 60% RH	40° C./ ambient	60° C./ ambient
0	98.68	98.68	98.68	98.68
2	97.67	100.60	98.87	99.92
4	97.40	100.50	98.97	99.06
8	98.40	99.56	98.83	97.74
12	97.17	98.47	97.13	94.97
26	97.90	96.40	99.00	93.50
52	N/A	N/A	N/A	N/A

Based on the powder in bottle stability at accelerated conditions (25° C./60% RH, 40° C./ambient, 60° C./ambient), it was determined that the enalapril/mannitol formulation was the most stable.

Example 2

Stability of Prepared Enalapril Solution

Enalapril Solution Formulation:

1.0 mg/mL enalapril solutions were prepared from the lactose and mannitol granulations (Example 1) made with the addition of OraSweet SF® flavored syrup and placed under refrigerated, 25° C./60% RH and 40° C./ambient conditions. A enalapril/sucrose solution was prepared at 2 mg/mL concentration to evaluate the effect of the higher concentration on solution stability. The following tables depict the stability of enalapril+stability agent solution in the various storage conditions.

US 8,568,747 B1

23

1 mg/mL Enalapril/Lactose Prepared Solution			
Time (Weeks)	Refrigerated	25° C./60% RH	40° C./ambient
0	101.66	101.66	101.66
1	100.63	100.33	97.18
2	101.35	99.77	93.69
3	101.25	98.68	90.03
4	100.65	97.25	86.21
8	101.27	94.19	73.69
12	102.15	92.99	65.91

1 mg/mL Enalapril/Mannitol Prepared Solution			
Time (Weeks)	Refrigerated	25° C./60% RH	40° C./ambient
0	95.86	95.86	95.86
1	94.56	94.08	91.28
2	94.98	93.90	87.48
3	95.06	92.59	83.86
4	94.42	91.28	80.45
8	95.10	88.39	68.52
12	95.74	86.99	60.43

2 mg/mL Enalapril/Sucrose Prepared Solution			
Time (Weeks)	Refrigerated	25° C./60% RH	40° C./ambient
0	99.16	99.16	99.16
2	101.1	98.71	89.05
4	101.3	95.48	79.86
8	99.79	90.35	62.94
12	99.40	86.18	40.24

In the prepared solutions, the enalapril+mannitol solution was most stable at 40° C./ambient conditions.

Example 3

Direct Blend Enalapril Powder Compositions

Enalapril Powder Composition A:

An enalapril powder composition as set forth in the following table is prepared.

Component	Amount in 150 mL Bottle (mg)	Weight (% w/w solids)
Enalapril Maleate	150	14.29
Mannitol	900	85.71
Total Solids	1050	100.0

The composition is prepared by adding the components together. The powder is then screened and direct blended until blend uniformity.

Enalapril Powder Composition B:

An enalapril powder composition as set forth in the following table is prepared.

24

Component	Amount in 150 mL Bottle (mg)	Weight (% w/w solids)
Enalapril Maleate	150	14.29
Mannitol	890	84.76
Colloidal Silicon Dioxide	10	0.95
Total Solids	1050	100.0

The composition is prepared by adding the components together. The powder is then screened and direct blended until blend uniformity.

Enalapril Powder Composition C:

An enalapril powder composition as set forth in the following table is prepared.

Component	Amount in 150 mL Bottle (mg)	Weight (% w/w solids)
Enalapril Maleate	150	14.29
Mannitol	590	56.19
Colloidal Silicon Dioxide	10	0.95
Sorbitol	300	28.57
Total Solids	1050	100.0

The composition is prepared by adding the components together. The powder is then screened and direct blended until blend uniformity.

Enalapril Powder Composition D:

An enalapril powder composition as set forth in the following table is prepared.

Component	Amount in 150 mL Bottle (mg)	Weight (% w/w solids)
Enalapril Maleate	150	12.5
Mannitol	590	49.17
Colloidal Silicon Dioxide	10	0.83
Sorbitol	300	25.0
Wild Cherry Flavor	150	12.5
Total Solids	1200	100.0

Enalapril Powder Composition E:

An enalapril powder composition as set forth in the following table is prepared.

Component	Amount in 150 mL Bottle (mg)	Weight (% w/w solids)
Enalapril Maleate	150	7.5
Mannitol	590	29.5
Colloidal Silicon Dioxide	10	0.5
Sorbitol	300	15
Sodium Bicarbonate	800	40
Lemon Flavor	150	7.5
Total Solids	2000	100.0

US 8,568,747 B1

25

Example 4

Enalapril Composition Scale-Up Optimization Studies

Scale-Up Studies Investigated Blend and Bottle Content Uniformity

Blend and Bottle Content Uniformity of Enalapril Powder Composition A:

Enalapril Powder Composition A (150 mg enalapril, 900 mg mannitol/bottle) was scaled-up and the resultant formulation tested for blend and content uniformity. For blend uniformity, 10 1 g samples were taken from the blender (top front right, middle front right, bottom front, top front left, middle front left, top back right, middle back right, bottom back, top back left, and middle back left) by a suitable powder sampler at the below times.

Blend Uniformity - Enalapril Powder Composition A		
Blending Time (min)	Avg drug assay (%)	% RSD
10	96.0	2.80
15	96.6	2.13
20	99.5	3.69

Bottle content uniformity values were assessed via a hopper study after filling and capping the Enalapril Powder Composition blend into 150 mL bottles:

Bottle Content Uniformity - Enalapril Powder Composition A			
Time Point	Avg drug assay (%)	% RSD	Acc. Value (Limit ≤ 15)
Beginning	89.9	2.12	13.2
Middle	104.7	2.66	9.9
End	99.8	3.14	7.5

The content uniformity study revealed that some segregation of the powder composition could have occurred post-blending.

Blend Time Variation for Enalapril Powder Composition A:

Blend time was assessed for possibility of contributing to segregation of the powder composition. Blend time was shortened to 5 minutes and blend uniformity and bottle content uniformity was assessed as above:

Blend Uniformity - Enalapril Powder Composition A		
Blending Time (min)	Avg drug assay (%)	% RSD
5	96.7	1.25
Bottle Content Uniformity - Enalapril Powder Composition A		
Study	Avg drug assay (%)	% RSD
Content Uniformity	95.9	6.14
By Weight	97.7	6.69

The high % RSD was observed in the bottle content uniformity studies indicating variance in the filling and capping of the drug powder composition.

26

Blend time was changed back to 10 minutes in an attempt to optimize blend and fill, however, it was not successful.

Lengthening the blend time to 20, 30, 40 and 60 minutes revealed the following observations:

Blend Uniformity - Enalapril Powder Composition A		
Blending Time (min)	Visual Observation	Avg drug assay (%)
20	Homogenous	89.9, 102.8, 96.1
30	Small round balls segregating in blend	90.4, 90.1, 100.9
40	Small round balls segregating in blend and gradually increasing in proportion	105.4
60	Much greater and clear segregation of round balls in the blend	139.8; fines: 55.8

FIG. 1 shows a visual depiction of the enalapril powder composition A blended for 60 minutes. Thus, a lower blend time (e.g., about 10-20 minutes) is contemplated to be more optimal to prevent 'balling up' and segregation of the powder blend.

The scaled-up enalapril and mannitol powder compositions (Enalapril Powder Composition A and the like) were examined in reconstitution studies where 150 mL Ora-Sweet® SF sugar-free flavored syrup was to the powder compositions. Scaled-up enalapril and mannitol powder compositions such as Enalapril Powder Composition A did not dissolve in the syrup, but instead resulted in powder clumping and specking on the surface of the liquid, termed 'clouding'. Various enalapril and mannitol formulations were examined at different concentrations, which resulted in similar 'clouding'. FIG. 2A shows the clouding phenomenon from an exemplary enalapril and mannitol powder formulation.

Reconstitution of Neat Enalapril Powder in Bottle:

Due to the 'clouding' in the reconstitution as well as the uniformity issues in the scale-up studies of Enalapril Powder Composition A, neat enalapril, i.e., drug alone, without any excipients, was examined for scale-up bottle filling and subsequent reconstitution. It was observed that during reconstitution with 150 mL Ora-Sweet® SF sugar-free flavored syrup, the neat enalapril did not dissolve but floated on the surface of the liquid, even after 2 hours standing after reconstitution (FIG. 2B).

Colloidal Silicon Dioxide Addition to form Enalapril Powder Composition B:

Although colloidal silicon dioxide has been reported to decrease stability of enalapril (Rezende et al., Stability and Compatibility Study on Enalapril Maleate using Thermoanalytical Techniques, *J. Thermal Anal. & Calorimetry*, 2008 (93) 881-886), the addition of colloidal silicon dioxide to an enalapril powder composition during scale-up resulted in improved and acceptable blend uniformity and bottle content uniformity levels. Enalapril Powder Composition B (150 mg enalapril, 890 mg mannitol, 10 mg colloidal silicon dioxide/bottle) was scaled-up and the resultant formulation tested for blend and content uniformity as described above. The blend and content uniformity assays showed that the addition of colloidal silicon dioxide imparted uniformity in the powder composition:

US 8,568,747 B1

27

Blend Uniformity - Enalapril Powder Composition B		
Blending Time (min)	Avg drug assay (%)	% RSD
10	99.8	1.34
10	99.7	1.08
Bottle Content Uniformity - Enalapril Powder Composition B		
Study	Avg drug assay (%)	% RSD
Content Uniformity	102.6	1.98
Content Uniformity	98.5	2.77

In reconstitution studies, surprisingly, the addition of colloidal silicon dioxide resulted in a solution that, upon visual inspection, was truly dissolved and homogenous (FIG. 2C).

A lower amount of colloidal silicon dioxide was also studied (150 mg enalapril, 895 mg mannitol, 5 mg colloidal silicon dioxide/bottle). However the enalapril powder composition had lower flowability than that of enalapril powder composition B.

The stability of the enalapril powder and liquid composition with respect to the addition of colloidal silicon dioxide was analyzed in Example 6.

Example 5

Additional Reconstitution Methods and Studies

The overall mixing efficiency and solution/suspension drug concentration homogeneity was evaluated over a series of mixing methods and times.

Mixing Method A:

75 mL of Ora-Sweet® SF sugar-free flavored syrup was added to a 150 mL bottle of Enalapril Powder Composition B and the bottle was shaken vigorously. A second 75 mL of Ora-Sweet® SF syrup was subsequently added and the bottle was shaken vigorously.

Observations:

The resultant liquid contained entrapped air bubbles. It was determined that the bubbles would interfere with dosing as a variable volume of the liquid could be administered in dosing syringes for administration.

Mixing Method B:

75 mL of Ora-Sweet® SF sugar-free flavored syrup was added to a 150 mL bottle of Enalapril Powder Composition B and the bottle was gently swirled. A second 75 mL of Ora-Sweet® SF syrup was subsequently added and the bottle was gently swirled. The bottle was then inverted slowly for about 5 times.

Observations:

The gently swirling and subsequent inversions minimized the bubble formation. However, in a clinical trial similar to Example 7, it was observed that the subjects had received a lower dose (about 1.30 mg) of enalapril rather than standard 10 mg dosage. Based on this observation, it was determined that the mixing method did not introduce enough energy in the process and resulted in improper wetting and mixing of the powder.

Mixing Method C:

150 mL bottle of Enalapril Powder Composition B was first tapped on a hard surface to disperse any powder caking. 75 mL of Ora-Sweet® SF sugar-free flavored syrup was added to the 150 mL bottle and the bottle was shaken for specified time intervals (10, 20, 30, 45 and 60 seconds). A second 75 mL of Ora-Sweet® SF syrup was subsequently added and the bottle

28

was shaken for the specified time interval. Bubbles were allowed to dissipate (for at least one hour). Two samples were taken immediately after the second shaking. One sample was filtered through a 0.45 micron filter. A third sample was taken 1 h after the second shaking and after any bubbles dissipated from the liquid. The three samples were assayed by HPLC. The mixing and homogeneity results are as follows:

Mixing Method C: Enalapril by HPLC as % of 1 mg/mL			
Time (seconds)	Sample 1 (unfiltered)	Sample 2 (filtered)	Sample 3 (1 h)
2 x 10	101.3	101.2	101.2
2 x 20	100.9	100.8	100.8
2 x 30	101.5	101.3	101.1
2 x 45	101.6	101.7	101.7
2 x 60	100.9	100.9	101.1

Observations:

There was no perceived difference observed between filtered and unfiltered samples indicating that the reconstituted enalapril liquid is not a suspension. The addition of 75 mL of Ora-Sweet® SF syrup followed by shaking for 10 seconds and the addition of another 75 mL of Ora-Sweet® SF syrup followed by shaking for 10 seconds resulted in a homogenous solution. All longer shaking times produced equivalent results.

Example 6

Additional Stability Studies

Powder Stability:

Enalapril Powder Composition B and its reconstituted oral liquid form were further investigated in stability studies. 1050 mg enalapril Powder Composition B in 150 mL white plastic bottles were examined for stability in $25 \pm 2^\circ \text{C} / 60 \pm 5\% \text{RH}$ at up to 9 months and $40 \pm 2^\circ \text{C} / 75 \pm 5\% \text{RH}$ (accelerated) conditions at up to 6 months. At each given time point, enalapril and related substances were assayed via HPLC. The below tables depict stability of the powder at the various conditions.

Enalapril Powder Composition B - $25^\circ \text{C} / 60\% \text{RH}$			
Time (Months)	Enalapril (%)	Enalaprilat (%)	DKP (%)
0	97.8	0.05	0.02
1	98.6	0.05	0.03
2	97.6	0.12	0.05
3	98.6	0.06	0.07
6	96.8	0.09	0.11
9	98.6	0.12	0.15

Enalapril Powder Composition B - $40^\circ \text{C} / 75\% \text{RH}$			
Time (Months)	Enalapril (%)	Enalaprilat (%)	DKP (%)
0	97.8	0.05	0.2
1	97.9	0.12	0.23
2	96.8	0.15	0.32
3	97.2	0.16	0.42
6	96.2	0.18	0.63

US 8,568,747 B1

29

Enalapril Powder Composition B remained stable through 6 months under accelerated stability conditions and 9 months under ambient ($25\pm 2^\circ\text{C}/60\pm 5\%\text{RH}$) conditions at up to 9 months conditions with slight increase in the levels of enalaprilat and DPK. However, none of the total related impurities exceeded 5%. Stability at ambient conditions was also examined for two additional lots of Enalapril Powder Composition B. Similar results were observed for the levels of enalaprilat and DPK.

Reconstituted Liquid Stability:

Enalapril Powder Composition B was reconstituted in 150 mL bottles according to Mixing Method C (2×30 s of shaking) and stored at ambient conditions. Aliquots were taken during selected time points during the study period. The below tables depict stability of the reconstituted liquid at the various conditions.

Enalapril Reconstituted Liquid - Ambient			
Time (Weeks)	Enalapril (%)	Enalaprilat (%)	DKP (%)
0	97.4	0.43	0.04
2	96.8	0.73	0.08
4	96.9	0.87	0.08
8	95.4	1.35	0.12
12	93.7	2.22	0.17

After being reconstituted, the enalapril liquid was stable in ambient conditions with essentially unchanged values of its attributes, including microbial limits, preservative effectiveness and preservative assay up to the end of the study period (12 weeks).

Example 7

Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Liquid Vs Vasotec® 10 mg Tablets Under Fasted Conditions and 10 mg Enalapril Maleate Oral Liquid in Fed Conditions in Healthy Adults

The objectives of this single-dose, open-label, randomized, three-period, three-treatment, three-way crossover study were:

To assess the bioavailability of a test formulation of 10 mg oral liquid reconstituted from Enalapril Powder Composition B versus Vasotec® 10 mg enalapril tablets under fasted conditions in healthy adults

To assess the food effect on a test formulation of 10 mg oral liquid reconstituted from Enalapril Powder Composition B in healthy adults

Study Design:

Healthy adult subjects were to receive each of the following three treatments in a randomized fashion during three study periods:

Treatment A, Test Formulation: Enalapril maleate oral liquid reconstituted from Enalapril Powder Composition B via Mixing Method C (2×30 s of shaking), 10 mg/10 mL, administered under fasted conditions

Treatment B, Reference Product: Vasotec®, one 10 mg tablet, administered under fasted conditions

Treatment C, Test Formulation: Enalapril maleate oral liquid reconstituted from Enalapril Powder Composition B via Mixing Method C (2×30 s of shaking), 10 mg/10 mL, administered under fed conditions

30

Screening assessments were performed by the investigator or designee within 28 days prior to study start. Treatments A and B were to be administered after an overnight fast of at least 10 hours; Treatment C was to be administered following an overnight fast of at least 10 hours and an FDA standard high-calorie, high-fat breakfast meal beginning 30 minutes prior to administration of the study drug. Each dose was to be orally administered with 240 mL (8 fl. oz.) of room temperature tap water; after dosing, no food was allowed until 4 hours postdose. Each drug administration was separated by a wash-out period of ≥ 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Plasma pharmacokinetic (PK) samples were analyzed for enalapril and enalaprilat using a validated analytical method; appropriate PK parameters were calculated for each formulation using on-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Each subject was to receive a total of three single doses, one dose at each of three study periods; the duration of the study for each subject would be approximately 45 days.

Subject Criteria:

Subjects must have been a male or non-pregnant, non-breastfeeding female; 18 to 55 years of age; with body mass index (BMI) between 18 and 30 kg/m² and weight a minimum of 50 kg (110 lbs). Subjects were not to have a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results; and were not to have a history of chronic cough, hyperkalemia, renal insufficiency, renal artery stenosis, or angioedema related to previous treatment with an angiotensin-converting enzyme inhibitor.

Results

Various pharmacokinetic parameters are summarized below for enalapril and enalaprilat.

Mean PK Parameters Single 10 mg Doses					
C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (h * ng/mL)	AUC_{inf} (h * ng/mL)	$T_{1/2}$ (h)	C_{last} (ng/mL)
Treatment A - Enalapril					
58.0	0.87	102.6	103.7	1.70	0.460
Treatment B - Enalapril					
61.8	0.92	106.5	107.5	1.45	0.467
Treatment C - Enalapril					
31.3	1.21	88.47	88.70	1.34	0.507
Treatment A - Enalaprilat					
41.0	3.45	405.3	443.3	30.49	0.841
Treatment B - Enalaprilat					
44.5	3.51	417.1	455.9	30.78	0.860
Treatment C - Enalaprilat					
26.4	4.49	315.7	360.1	33.94	0.889

Concentration-time data are summarized graphically for enalapril in FIG. 3 (linear, top; log, bottom) and enalaprilat in FIG. 4 (linear, top; log, bottom).

US 8,568,747 B1

31

Test Formulation Versus Reference Product (Fasted):

Based on the geometric mean ratios of enalapril and enalaprilat AUCs (Test/Reference for AUC_{last} and AUC_{inf}), the bioavailability of the test formulation relative to the reference product was approximately 96% to 97%. The geometric mean ratios of enalapril and enalaprilat C_{max} were 92.45% and 90.94%, respectively. The 90% confidence intervals about the geometric mean ratios (Test/Reference) of enalapril and enalaprilat C_{max} and AUCs were within the accepted 80% to 125% range, indicating no significant difference.

Test Formulation (Fasted) Versus Test Product (Fed):

Based on the geometric mean ratios of enalapril AUCs (Fed/Fasted for AUC_{last} and AUC_{inf}), a high-fat meal decreases the bioavailability of enalapril from the test formulation by approximately 14% to 15%; C_{max} is decreased by approximately 46%. For enalaprilat, food decreases C_{max} by approximately 36% and AUCs by approximately 20% to 23%.

Clinical Trial with Mixing Method B:

The above trial was conducted with Enalapril maleate oral liquid reconstituted from Enalapril Powder Composition B via Mixing Method A (shake vigorously). The study was discontinued prior to dosing after it was observed that the mixing method created entrapped air bubbles in the liquid and could result in uneven dosing via dosing syringes.

Clinical Trial with Mixing Method B:

The above trial was conducted with Enalapril maleate oral liquid reconstituted from Enalapril Powder Composition B via Mixing Method B (gentle swirling and inversion). A number of subjects on the test product only were observed to have very low enalapril and enalaprilat levels in both fasted and fed test treatments. Based on this observation, the reconstituted enalapril maleate test formulation was assayed and it was determined that the test dose administered was not a 10 mg dose as specified in the study protocol, but was a mean dose of about 1.30 mg. Upon further investigation, it was determined that the low concentration of enalapril in the dose occurred due to the mixing method.

32

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A pharmaceutical powder that is reconstituted into an oral liquid formulation, the powder consisting of:
 - (a) about 14% (w/w) enalapril or a pharmaceutically acceptable salt thereof,
 - (b) about 85% (w/w) mannitol, and
 - (c) about 1% (w/w) colloidal silicon dioxide,
 wherein, when the powder is reconstituted into an oral liquid, the liquid is homogenous and stable for at least 12 weeks at about $25\pm 5^\circ\text{C}$. and $55\pm 10\%$ relative humidity.
2. The pharmaceutical powder of claim 1, wherein the enalapril or pharmaceutically acceptable salt thereof is enalapril maleate.
3. The pharmaceutical powder of claim 1, wherein the powder is reconstituted in water for the oral liquid.
4. The pharmaceutical powder of claim 1, wherein the powder is reconstituted in syrup for the oral liquid.
5. The pharmaceutical powder of claim 1, wherein the powder is stable for at least six months at ambient, accelerated or refrigerated conditions.
6. The pharmaceutical powder of claim 1, wherein the powder is 150 mg enalapril, 890 mg mannitol and 10 mg colloidal silicon dioxide.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,568,747 B1
APPLICATION NO. : 13/670355
DATED : October 29, 2013
INVENTOR(S) : Lian G. Rajewski et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page:

Item 75, please correct inventor's name from "Frank Seagrave" to --Frank Segrave--.

Signed and Sealed this
Twenty-eighth Day of January, 2014



Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**November 2003
ICH**

Revision 2

Guidance for Industry

Q1A(R2) Stability Testing of New Drug Substances and Products

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Center for Biologics Evaluation and Research (CBER)**

**November 2003
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Revision 2

*Contains Nonbinding Recommendations***TABLE OF CONTENTS**

I. INTRODUCTION (1)	1
A. Objectives of the Guidance (1.1)	1
B. Scope of the Guidance (1.2)	2
C. General Principles (1.3)	2
II. GUIDANCE (2)	2
A. Drug Substance (2.1)	2
1. General (2.1.1)	2
2. Stress Testing (2.1.2)	3
3. Selection of Batches (2.1.3)	3
4. Container Closure System (2.1.4)	3
5. Specification (2.1.5)	3
6. Testing Frequency (2.1.6)	4
7. Storage Conditions (2.1.7)	4
8. Stability Commitment (2.1.8)	6
9. Evaluation (2.1.9)	7
B. Drug Product (2.2)	8
1. General (2.2.1)	8
2. Photostability Testing (2.2.2)	8
3. Selection of Batches (2.2.3)	8
4. Container Closure System (2.2.4)	8
5. Specification (2.2.5)	9
6. Testing Frequency (2.2.6)	9
7. Storage Conditions (2.2.7)	10
8. Stability Commitment (2.2.8)	14
9. Evaluation (2.2.9)	15
10. Statements/Labeling (2.2.10)	16
GLOSSARY (3)	17
REFERENCES (4)	21
ATTACHMENT List Of Revision 2 Changes	22

Contains Nonbinding Recommendations

Guidance for Industry¹

**Q1A(R2) Stability Testing of New Drug
Substances and Products**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1)²

This guidance is the second revision of *Q1A Stability Testing of New Drug Substances and Products*, which was first published in September 1994 and revised in August 2001. The purpose of this revision is to harmonize the intermediate storage condition for zones I and II with the long-term condition for zones III and IV recommended in the ICH guidance *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV*. The changes made in this second revision are listed in the attachment to this guidance.

A. Objectives of the Guidance (1.1)

This guidance is intended to define what stability data package for a new drug substance or drug product is sufficient for a registration application within the three regions of the European Union (EU), Japan, and the United States. It does not seek to address the testing for registration in or export to other areas of the world. The guidance exemplifies the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

¹ This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document was endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

² Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at *Step 4* of the ICH process.

Contains Nonbinding Recommendations

B. Scope of the Guidance (1.2)

The guidance addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guidance does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, or clinical trial applications.

Specific details of the sampling and testing for particular dosage forms in their proposed container closures are not covered in this guidance.

Further guidance on new dosage forms and on biotechnological/biological products can be found in ICH guidances *Q1C Stability Testing for New Dosage Forms* and *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*, respectively.

C. General Principles (1.3)

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The choice of test conditions defined in this guidance is based on an analysis of the effects of climatic conditions in the three regions of the EU, Japan, and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guidance addresses climatic zones I and II. The principle has been established that stability information generated in any one of the three regions of the EU, Japan, and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guidance and the labeling is in accord with national/regional requirements.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. GUIDANCE (2)

A. Drug Substance (2.1)

1. General (2.1.1)

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

Contains Nonbinding Recommendations**10. *Statements/Labeling (2.1.10)***

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as *ambient conditions* or *room temperature* should be avoided.

A retest period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

B. Drug Product (2.2)**1. *General (2.2.1)***

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance, results from stability studies on the drug substance, and experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

2. *Photostability Testing (2.2.2)*

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B.

3. *Selection of Batches (2.2.3)*

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Other supporting data can be provided.

4. *Container Closure System (2.2.4)*

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and

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When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs (i.e., matrixing or bracketing), where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified.

7. *Storage Conditions (2.2.7)*

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points, and if full shelf life, long-term data will not be available before submission, at 12 months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below. The general case should apply if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

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a. General case (2.2.7.1)

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and *significant change* occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

In general, *significant change* for a drug product is defined as one or more of the following (as appropriate for the dosage form):

- A 5 percent change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures
- Any degradation product's exceeding its acceptance criterion
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions.
- Failure to meet the acceptance criterion for pH
- Failure to meet the acceptance criteria for dissolution for 12 dosage units

b. Drug products packaged in impermeable containers (2.2.7.2)

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

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c. Drug products packaged in semipermeable containers (2.2.7.3)

Aqueous-based products packaged in semipermeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semipermeable containers can withstand low relative humidity environments. Other comparable approaches can be developed and reported for nonaqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term *	25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/not more than (NMT) 25% RH	6 months

* It is up to the applicant to decide whether long-term stability studies are performed at 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.

** If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

When long-term studies are conducted at 25°C ± 2°C/40% RH ± 5% RH and significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be performed, as described under the general case, to evaluate the temperature effect at 30°C. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40 percent RH.

A 5 percent loss in water from its initial value is considered a significant change for a product packaged in a semipermeable container after an equivalent of 3 months' storage at 40°C/NMT 25 percent RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5 percent or more after an equivalent of 3 months' storage at 40°C/NMT 25 percent RH may be appropriate if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long-term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation

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coefficient for a container closure system can be experimentally determined by using the worst case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature (e.g., 40°C), the calculated water loss rate during storage at NMT 25 percent RH is the water loss rate measured at 75 percent RH multiplied by 3.0, the corresponding water loss rate ratio.

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

d. Drug products intended for storage in a refrigerator (2.2.7.4)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

If the drug product is packaged in a semipermeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-term storage condition.

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If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipment and handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

- e. Drug products intended for storage in a freezer (2.2.7.5)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20°C ± 5°C	12 months

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

- f. Drug products intended for storage below -20°C (2.2.7.6)

Drug products intended for storage below -20°C should be treated on a case-by-case basis.

8. *Stability Commitment (2.2.8)*

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies postapproval to firmly establish the shelf life.

Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.
- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

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- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

9. *Evaluation (2.2.9)*

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (e.g., dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95 percent one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of the degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

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Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time if justified. This justification should be based, for example, on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, and/or existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

10. Statements/Labeling (2.2.10)

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing. Terms such as *ambient conditions* or *room temperature* should be avoided.

There should be a direct link between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label.

*Contains Nonbinding Recommendations***GLOSSARY (3)**

The following definitions are provided to facilitate interpretation of the guidance.

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer term chemical effects at nonaccelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Bracketing: The design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, package size) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Climatic zones: The four zones in the world that are distinguished by their characteristic, prevalent annual climatic conditions. This is based on the concept described by W. Grimm (*Drugs Made in Germany*, 28:196-202, 1985 and 29:39-47, 1986).

Commitment batches: Production batches of a drug substance or drug product for which the stability studies are initiated or completed postapproval through a commitment made in the registration application.

Container closure system: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage form: A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance: The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient: Anything other than the drug substance in the dosage form.

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Expiration date: The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Formal stability studies: Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period of a drug substance or the shelf life of a drug product.

Impermeable containers: Containers that provide a permanent barrier to the passage of gases or solvents (e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions).

Intermediate testing: Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long-term at 25°C.

Long-term testing: Stability studies under the recommended storage condition for the retest period or shelf life proposed (or approved) for labeling.

Mass balance: The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 percent of the initial value, with due consideration of the margin of analytical error.

Matrixing: The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Mean kinetic temperature: A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (*J. Pharm. Sci.*, 60:927-929, 1971) can be used.

New molecular entity: An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or noncovalent bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pilot scale batch: A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For

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solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is larger.

Primary batch: A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch: A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Retest date: The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Retest period: The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics.

Semipermeable containers: Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial pressure gradient. Examples of semipermeable containers include plastic bags and semirigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification: See ICH Q6A and Q6B.

Specification, Release: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

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Specification, Shelf life: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period, or that a drug product should meet throughout its shelf life.

Storage condition tolerances: The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guidance. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress testing (drug substance): Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product): Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing of certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting data: Data, other than those from formal stability studies, that support the analytical procedures, the proposed retest period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of drug substance, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

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REFERENCES (4)³

ICH Q1B Photostability Testing of New Drug Substances and Products

ICH Q1C Stability Testing for New Dosage Forms

ICH Q3A Impurities in New Drug Substances

ICH Q3B Impurities in New Drug Products

ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products

ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

ICH Q6B Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at <http://www.fda.gov/cder/guidance/index.htm>

18

Buffers and pH Adjusting Agents

Melgardt de Villiers, PhD

CHAPTER OUTLINE

Definitions

Uses of Buffers and pH Adjusting Agents

Buffer Capacity

Selecting a Buffer System or a Compound to Adjust pH

Acidifying, Alkalizing, and Buffering Agents

I.

DEFINITIONS

A. An **acid** may be defined as

1. A substance that, when dissolved in water, yields hydrogen ions, H^+ (Arrhenius theory).
2. A species that yields protons, H^+ (Bronsted-Lowry theory).
3. An electron pair acceptor (Lewis theory).

B. A **base** may be defined as

1. A substance that, when dissolved in water, gives hydroxide ions, OH^- (Arrhenius theory).
2. A species that can accept a proton (Bronsted-Lowry theory).
3. An electron pair donor (Lewis theory).

In pharmaceutical systems, we usually are dealing with solutions that contain water; therefore, the Arrhenius and Bronsted-Lowry definitions are most suitable for our purposes.

C. A **buffer** is a compound or a mixture of compounds that, when present in a solution, resists changes in the pH of the solution when small quantities of acid or base are added to the solution.

D. **Buffer capacity** is a measure of the resistance to change in the pH of a solution when acids or bases are added to the solution.

E. Many useful equations have been derived to deal with the subject of acid-base chemistry. A list of those equations most useful in pharmaceutical systems is given in Table 18.1. Example calculations using these equations are also given.

II.

USES OF BUFFERS AND pH ADJUSTING AGENTS

Buffers or agents to adjust the pH of solutions may be added to manufactured pharmaceutical products or to extemporaneously compounded preparations for any of the following reasons:

- A. For preparations that are intended to be applied to the sensitive membranes of the eye or nasal passages or that may be injected into muscles, blood vessels, organs, tissue, or lesions, it is desirable to adjust the pH of the preparation to a level that is close to the physiologic pH of the tissue. This is done to minimize tissue damage and pain or discomfort experienced by the patient.
- B. The absorption, and therefore the therapeutic effectiveness, of certain drugs may be improved when they are present either in an ionized or nonionized state. This state may be manipulated and maintained by adjusting the pH of the medium.
- C. The chemical stability of many drugs in solution may be improved by maintaining the pH of the solution in a particular range.
- D. The aqueous solubility of many organic drugs depends on the degree to which these weak electrolytes are present in ionic form. This, in turn, may depend on the pH of the solution.

III.

BUFFER CAPACITY

- A. Buffer capacity, β , is defined by the formula:

$$\beta = \frac{\Delta B}{\Delta pH}$$

where ΔB is the gram equivalents per liter of strong acid or strong base added to the buffer solution and ΔpH is the resulting pH change. The larger β is, the greater the buffer capacity of the system (that is, its ability to resist a pH change).

- B. While buffer capacity can be determined for a system by using the formula just given, it is not often calculated in compounding situations. Because of the limited beyond-use datings needed for compounded drug preparations, exact buffer capacities are not required. For a detailed treatment of the subject of buffer capacity, refer to a book on physical pharmacy (1).
- C. Even though we rarely calculate buffer capacity, it is helpful to understand the concept in principle and to understand the circumstances under which buffer capacity is maximized.
 - 1. Solutions of strong acids such as HCl will resist a change in pH at or below pH 3. In fact, the standard buffer solution identified by the USP for the pH range 1.2 to 2.2 is a 0.2 M solution of HCl to which KCl has been added as a neutral salt for proper electrolyte concentration (2).
 - 2. Similarly, strong bases such as NaOH give good buffer capacity at pH 11 or higher.
 - 3. The most common buffer systems consist of a combination of a weak acid and its salt (i.e., its conjugate base) or a weak base and its salt (i.e., its conjugate acid).
 - a. The Henderson-Hasselbalch equation, also known as the *buffer equation*, relates the pH of a solution, which contains an acid-base conjugate pair, to the pair's dissociation constant and the concentrations of the species in the solution. This equation and sample problems are shown in Table 18.1.
 - b. Acid-base conjugate pairs have their greatest buffer capacity when the pH of the solution is equal to their pK_a , and buffer capacity of an acid-base pair is effective in the range $pH = pK_a \pm 1$.
 - 4. Buffer capacity is related to the concentration of the buffer; the greater the concentration of the buffer, the greater the resistance to a change in pH.
 - 5. High buffer capacity is sometimes undesirable. For example, when a drug is most stable at a pH that differs considerably from the physiologic pH at the site of administration, a compromise must be found. One possible solution is to use a buffer that maintains the pH at the desirable level for stability but has a relatively low buffer capacity, so that on administration, the body's natural buffering systems will rapidly alter the pH of the solution to a more comfortable level.

IV.

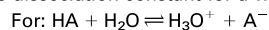
SELECTING A BUFFER SYSTEM OR A COMPOUND TO ADJUST pH

- A. First, consider the route of administration for the dosage form.
 - 1. Ingredients to buffer or adjust pH must be nontoxic for the intended route of administration. This is an important factor to consider. For example, boric acid and sodium borate are common ingredients for ophthalmic solutions; these would not be satisfactory for systemic drug preparations because borate is toxic systemically.
 - 2. Agents for any route of administration should be nonirritating at the needed concentration.
 - 3. For oral liquid preparations, buffer compounds should not have a disagreeable odor or taste.
 - 4. Agents used for parenteral preparations must be in sterile form or must be rendered sterile.

Table 18.1**EQUATIONS USEFUL IN ACID-BASE AND BUFFER CALCULATIONS****GENERAL EQUATIONS DEFINING pH AND pK**

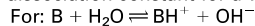
$$\begin{aligned} \text{pH} &= -\log [\text{H}_3\text{O}^+] \\ \text{pOH} &= -\log [\text{OH}^-] \\ \text{pH} + \text{pOH} &= \text{pK}_w = 14 \\ \text{pK}_a &= -\log K_a \\ \text{pK}_b &= -\log K_b \\ \text{pK}_a + \text{pK}_b &= \text{pK}_w = 14 \end{aligned}$$

K_a is the dissociation constant for a weak acid.



$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]}$$

K_b is the dissociation constant for a weak base



$$K_b = \frac{[\text{BH}^+][\text{OH}^-]}{[\text{B}]}$$

Generally K values for all drugs, both acids and bases, are now reported as K_a s.

SPECIFIC EQUATIONS**EXAMPLES**

For a strong acid:
 $\text{pH} = -\log [\text{C}_a] = -\log [\text{H}^+]$

0.1 N HCl
 $\text{pH} = -\log [\text{C}_a] = -\log [0.1] = 1$

For a strong base:
 $\text{pOH} = -\log [\text{OH}^-] = -\log [\text{C}_b]$
 or $\text{pH} = \text{pK}_w + \log [\text{C}_b]$

0.1 N NaOH
 $\text{pH} = \text{pK}_w + \log [\text{C}_b] = 14 + \log [0.1]$
 $= 14 - 1 = 13$

For a weak acid:
 $\text{pH} = \frac{1}{2} \text{pK}_a - \frac{1}{2} \log [\text{C}_a]$

0.1 N acetic acid HOAc; $\text{pK}_a = 4.76$
 $\text{pH} = \frac{1}{2} (4.76) - \frac{1}{2} \log [0.1]$
 $= 2.38 - (-0.5) = 2.88$

For a weak base:
 $\text{pOH} = \frac{1}{2} \text{pK}_b - \frac{1}{2} \log [\text{C}_b]$ or
 $\text{pH} = \frac{1}{2} \text{pK}_w + \frac{1}{2} \text{pK}_a + \frac{1}{2} \log [\text{C}_b]$

0.1 N sodium acetate (the conjugate base of acetic acid) NaOAc
 $\text{pH} = 7 + 2.38 + \frac{1}{2} \log [0.1] = 8.88$

For a diprotic (H_2A) acid:
 Solution with only the acid
 $\text{pH} = \frac{1}{2} \text{pK}_{a1} - \frac{1}{2} \log [\text{C}_a]$
 Notice that this is the same equation as for a weak acid.

0.1 M carbonic acid H_2CO_3 ; $\text{pK}_{a1} = 6.37$; $\text{pK}_{a2} = 10.33$
 $\text{pH} = \frac{1}{2} (6.37) - \frac{1}{2} \log [0.1]$
 $= 3.185 - (-0.5) = 3.685$

For a diprotic (H_2A) acid:
 Solution with only the ampholyte HA^-
 $\text{pH} = \frac{1}{2} \text{pK}_{a1} + \frac{1}{2} \text{pK}_{a2}$

0.1 M sodium bicarbonate NaHCO_3
 $\text{pH} = \frac{1}{2} (6.37) + \frac{1}{2} (10.33)$
 $= 3.185 + 5.165 = 8.35$

For a diprotic (H_2A) acid:
 Solution with only the diacidic base, A^{2-}
 $\text{pH} = \frac{1}{2} \text{pK}_w + \frac{1}{2} \text{pK}_{a2} + \frac{1}{2} \log [\text{C}_b]$

0.1 M sodium carbonate Na_2CO_3
 $\text{pH} = \frac{1}{2} (14) + \frac{1}{2} (10.33) + \frac{1}{2} \log (0.1)$
 $= 7 + 5.165 + (-0.5) = 11.67$

For conjugate acid-base pairs:
 $\text{pH} = \text{pK}_a + \log \frac{[\text{conjugate base}]}{[\text{conjugate acid}]}$

Ex. #1: 0.1 M HOAc and 0.1 M NaOAc
 $\text{pH} = 4.76 + \log \frac{[0.1]}{[0.1]} = 4.76 + \log 1$
 $= 4.76 + 0 = 4.76$

For acids this is often written:
 $\text{pH} = \text{pK}_a + \log \frac{[\text{salt}]}{[\text{acid}]}$

Ex. #2: 0.1 M HOAc and 0.2 M NaOAc
 $\text{pH} = 4.76 + \log \frac{[0.2]}{[0.1]} = 4.76 + 0.30$
 $= 5.06$

For bases this is often written:
 $\text{pH} = \text{pK}_a + \log \frac{[\text{base}]}{[\text{salt}]}$

Ex. #3: 0.1 M ammonia NH_4OH and 0.1 M ammonium chloride NH_4Cl
 $\text{pK}_b = 4.76$ pK_a (for conjugate acid) = 9.24
 $\text{pH} = 9.24 + \log \frac{[0.1]}{[0.1]} = 9.24$

These are all equivalent forms of the Henderson-Hasselbalch equation.

Ex. #4: 0.1 M NH_4OH and 0.2 M NH_4Cl
 $\text{pH} = 9.24 + \log \frac{[0.1]}{[0.2]} = 9.24 - 0.30 = 8.94$

Note: You may recall from previous coursework that the equations presented in this table are simplified versions of more complex (and more accurate) equations. They are based on assumptions that do not hold in all cases. (For example, $\text{pK}_w = 14$ only at 25°C.) They do give the sort of approximations that are helpful in the practical situations encountered in compounding. For a detailed treatment of this subject, the reader may wish to review chapters on ionic equilibria and buffered and isotonic solutions in a book on physical pharmacy (1) or an equivalent text.

Table 18.2

MODIFIED WALPOLE ACETATE BUFFER

pH	ACETIC ACID 99% (mL/100 mL)	SODIUM ACETATE ANHYDROUS (g/100 mL)	SODIUM CHLORIDE TO MAKE ISOTONIC (g/100 mL)
3.6	1.11	0.123	0.28
3.8	1.06	0.197	0.28
4.0	0.98	0.295	0.27
4.2	0.88	0.435	0.26
4.4	0.76	0.607	0.24
4.6	0.61	0.804	0.22
4.8	0.48	0.984	0.21
5.0	0.35	1.156	0.19
5.2	0.25	1.296	0.18
5.4	0.17	1.402	0.17
5.6	0.11	1.484	0.16

Note: This buffer is suitable for internal, external, or ophthalmic use.

Source: Reprinted with permission from Schumacher GE. Buffer formulations. Am J Hosp Pharm 1966; 23: 629.

- Ophthalmic solutions are ordinarily buffered at the pH of maximum stability for the drugs they contain, but if this pH is more than 1 pH unit from neutrality (i.e., outside the range of 6.5 to 8.5), a system with a low buffer capacity should be used (3) so that when the ophthalmic solution is dropped into the eye, the buffer system of the tears will quickly bring the pH of the solution back to that of the tears. Generally, a buffer capacity less than 0.05 is desired with a pH in the range of 4 to 8 (4,5). See Chapter 33 for more details on pH and buffering considerations for ophthalmic solutions.

B. Consider the easiest systems first.

- If a formula merely calls for the adjustment of pH to a given level, usually a dilute solution (0.1 to 0.2 N) of HCl or NaOH may be used. Be aware of possible compatibility considerations with the chloride ion in HCl. For example, if a drug is available as a salt with an uncommon anion, such as mesylate, the chloride may cause precipitation because the hydrochloride salt of that drug is less soluble; the preservatives phenylmercuric acetate and nitrate precipitate with halides, etc.
- Sodium Bicarbonate Injection is often used to raise the pH of some parenteral preparations. It is sterile and nontoxic, but it too may have compatibility issues. Always check for compatibility with all formulation components.
- For oral or topical liquids, consider using a preformulated vehicle. Many of the available flavored syrups and liquid vehicles contain buffers or ingredients that function as buffers. See Chapter 22, Vehicles for Liquid Preparations, for descriptions and specifications, and examples in Sample Prescriptions 28.5 and 28.6 in Chapter 28 and 30.7 in Chapter 30 of this book.
- For an easily made buffer in the low- to mid-pH range (3.6 to 5.6), the Acetate Buffer given in Table 18.2 is useful (6). It may be used for systemic, topical, or ophthalmic drug preparations. If isotonicity is needed, the appropriate quantities of sodium chloride are also given; if any of the preparation ingredients are incompatible with halides, sodium nitrate or dextrose in equal osmolar quantities (see Chapter 11) can be substituted for the sodium chloride.
- For preparations to be buffered between pH 6 and 8, Sorensen's Phosphate Buffer is a useful system. It can be used for systemic, topical, or ophthalmic preparations. Its formula is shown in Table 18.3 (7,8). It has a relatively high buffer capacity. If an isotonic solution is needed, sodium chloride in the amounts given in the table can be added; if any of the preparation ingredients are incompatible with halides, sodium nitrate or dextrose in equal osmolar quantities (see Chapter 11) can be substituted for the sodium chloride. The use of this buffer in an ophthalmic solution is illustrated in Sample Prescription 33.2 in Chapter 33.
- If a **concentrated** multi-purpose buffer solution is desired in the low- to mid-pH range (2.5 to 6.5), the Citrate Buffer in Table 18.4 can be used. When combined in the ratios given, the resulting solution has a molarity of 0.33 M. This buffer can be diluted 10-fold and still have adequate buffer capacity (6).
- For ophthalmic solutions that require buffering in the mid-acid range (~5), an aqueous solution of Boric Acid 1.9% is isotonic, easy to make, and has an appropriately low buffer capacity

Table 18.3

SORENSEN'S MODIFIED PHOSPHATE BUFFER

ACID STOCK SOLUTION, M/15 SODIUM BIPHOSPHATE		ALKALINE STOCK SOLUTION, M/15 SODIUM PHOSPHATE	
*Sodium Biphosphate, Anhydrous	8.006 g	Sodium Phosphate, Anhydrous	9.473 g
Purified Water, qs ad	1,000 mL	Purified Water, qs ad	1,000 mL
mL OF M/15 SODIUM BIPHOSPHATE SOLUTION	mL OF M/15 SODIUM PHOSPHATE SOLUTION	pH	SODIUM CHLORIDE REQUIRED FOR ISOTONICITY (g/100 mL)
90	10	5.9	0.52
80	20	6.2	0.51
70	30	6.5	0.50
60	40	6.6	0.49
50	50	6.8	0.48
40	60	7.0	0.46
30	70	7.2	0.45
20	80	7.4	0.44
10	90	7.7	0.43
5	95	8.0	0.42

*Sodium biphosphate, monohydrated 9.208 g may be used.

This buffer is suitable for internal, external, or ophthalmic use.

Source: Deardorff DL. Ophthalmic solutions. In: Hoover JE, ed. Remington's pharmaceutical sciences, 14th ed. Easton, PA: Mack Publishing Co., 1970; 1553–1555. Sørensen SL. Enzyme studies. II. The measurement and importance of the hydrogen ion concentration in enzyme reactions. Biochem Z 1909; 21: 131 and 22: 352.

Table 18.4

CONCENTRATED MULTI-PURPOSE BUFFER SOLUTION (CITRATE BUFFER)

ACID STOCK SOLUTION, M/3 CITRIC ACID		ALKALINE STOCK SOLUTION, M/3 SODIUM CITRATE	
*Citric Acid Monohydrate	70 g	Sodium Citrate Dihydrate	98 g
Purified Water, qs ad	1,000 mL	Purified Water, qs ad	1,000 mL
*Citric Acid Anhydrous 64 g may be substituted			
mL OF M/3 CITRIC ACID SOLUTION	mL OF M/3 SODIUM CITRATE SOLUTION		pH
92	8		2.5
82	18		3.0
68	32		3.5
58	42		4.0
44	56		4.5
28	72		5.0
14	86		5.5
6	94		6.0
2	98		6.5

Both compounds combined yield a concentration of 0.33 M.

This buffer is suitable for internal, external, or ophthalmic use.

Table 18.5

PALITZSCH OPHTHALMIC BUFFER

ACID STOCK SOLUTION		ALKALINE STOCK SOLUTION	
Boric Acid	12.404 g	Sodium Borate Decahydrate	19.108 g
Purified Water, q.s. ad	1,000 mL	Purified Water, q.s. ad	1,000 mL
mL OF 0.2 M BORIC ACID SOLUTION		mL OF 0.05 M SODIUM BORATE SOLUTION	pH
97		3	6.8
94		6	7.1
90		10	7.4
85		15	7.6
80		20	7.8
75		25	7.9
70		30	8.1
65		35	8.2
55		45	8.4
45		55	8.6
40		60	8.7
30		70	8.8
20		80	9.0
10		90	9.1

Source: Palitzsch S. Use of borax and boric acid solutions in the colorimetric measurement of the hydrogen ion concentration of sea water. *Biochem Z* 1915; 70: 333.

for this situation. Its use is illustrated in Sample Prescription 33.1 in Chapter 33. An example of a borate buffer system at higher pH, the Palitzsch buffer, is given in Table 18.5 (9). Numerous other borate buffers are reported in the literature (7,10–12).

C. If a customized buffer solution must be made, follow these steps:

1. Select a compound or combination of compounds that can give you a pH in the range you desire.
 - a. As discussed earlier, this may be a strong acid, a strong base, or a conjugate pair. If using a conjugate pair, the pK_a of the conjugate acid should be within one pH unit of the desired pH.
 - b. For possible conjugate pairs, you may want to consult the table in the appendix section of the CD that accompanies this book. This table gives the pK_a s of a large number of drugs and reference compounds.
 - c. Be sure that your choice is chemically stable, is sufficiently soluble, is compatible with the other ingredients in the formulation, is free from odor and color, and is nonsensitizing and nontoxic by the route of administration being used.
 - d. Examples of some possible choices are given in Table 18.6.

Table 18.6

BUFFER CHOICES FOR SPECIFIC pH RANGES

pH RANGE	BUFFER
pH 1–3	HCl
pH 2.5–6.5	Citrate Buffer
pH 3.6–5.6	Acetate Buffer
pH 6–8	Sorenson's Phosphate Buffer
pH 8–9	Sodium Bicarbonate
pH 9–11	Sodium Bicarbonate/Sodium Carbonate
pH 11–13	NaOH



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Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations

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Abstract

The chemical stability of enalapril maleate in tablet dosage forms consisting of different formulation excipients has been studied in this work. The influence of various parameters such as heat, moisture, light and the drug-matrix was investigated. The degradation of enalapril maleate has been followed by using an HPLC method, which was demonstrated to be specific, stability indicating, accurate and precise. The degradation kinetics of enalapril maleate in phosphate buffer solutions of pH values in the range of 2.2–10.5 were observed to be pseudo first order throughout the whole pH range studied. Enalapril maleate alone showed high stability for temperature under dry and humid conditions, however it became unstable when mixed with the drug-matrix in its tablet formulations and exposed to the same conditions. The pathway of degradation of enalapril maleate was found to be pH dependent. The extent of degradation of two different enalapril maleate tablet formulations (product A of a basic drug-matrix and product B of an acidic drug-matrix) has been investigated. The degree of degradation of the product with acidic matrix was significantly less than that of the basic matrix under same temperature and humidity conditions. Infact, diketopiperazine and enalaprilat degradants were mainly associated with the degradation of the product with the acidic matrix and that with the basic matrix, respectively. Dry enalapril maleate powder showed some photolysis, which was more significant with daylight (3.3%) compared with that under UV light (0.2%). Although the product with the acidic matrix showed some photolysis but the effect was not pronounced and the % recovery of enalapril was almost complete and within the acceptable experimental errors. However, the product with the basic matrix showed almost no response for photolysis. © 2001 Elsevier Science B.V. All rights reserved.

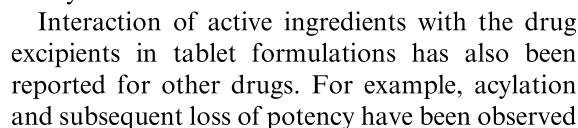
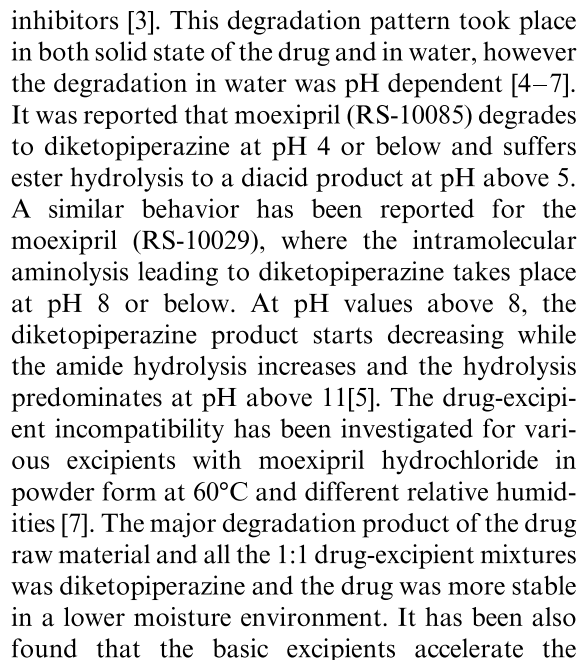
Keywords: Enalapril maleate; Lubricating agents; Enalaprilat; Diketopiperazine; Drug stability; HPLC

1. Introduction

Enalapril maleate, angiotensin-converting enzyme inhibitor, is 1- $\{N-[(s)-1\text{-carboxyl-3-phenyl-propyl}]\text{-L-alanyl}\}$ -L-proline 1-ethyl ester maleate with the following structural formula,

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for aspirin-codeine [8] and aspirine–phenylephrine [9] combinations.

The effect of various formulation factors such as the type of excipient and packaging materials, temperature, light, pH of the matrix and humidity play an important role in the product design. Consequently, the influence of formulation factors should be considered during stability studies. This work aimed at studying the effect of two different types of tablet formulations (formulations with acidic and basic matrices) on the stability and pathway of degradation of enalapril maleate in solid matrices and tablets with respect to temperature and humidity. Furthermore, the effect of light on the stability of enalapril maleate alone and in tablet formulations was also investigated.

2. Experimental

2.1. Materials and instrumentation

Enalapril maleate of USP grade was obtained from JPM, Jordan. The excipients used were of pharmaceutical grades (USP or BP). All chemicals were of analytical or HPLC grade. Enalapril maleate, diketopiperazine, enalaprilat, enalapril lactone I and enalapril lactone II were supplied by JPM. Two commercial products of enalapril maleate tablets, product A (the tablet comprises 20 mg enalapril maleate, lactose, starch, magnesium stearate, red iron oxide, yellow iron oxide and sodium bicarbonate with aluminium/aluminium packaging material) and product B (the tablet comprises 20 mg enalapril maleate, lactose, starch and triglyceride palmitic acid with PVC/aluminum packaging material) were obtained from the Jordan market.

High performance liquid chromatograms have been run on a Du Pont Instrument/Series 8800 equipped with the Merck column, Lichrosphere C₈, 250 × 4.6 mm of 5 µm.

Ultraviolet rays sterilizer (AH POONG AP602) connected to germicidal lamp G15T8-AN 15W (SANKYO DENKI, Japan) was used to study the photolysis of enalapril maleate and the tablet formulations.

2.2. Chromatographic method

The standard USP HPLC method [10] in which the column oven was kept at 65°C has been employed. The mobile phase used was a mixture of phosphate buffer (pH 2)–acetonitrile (17:8, v/v). Phosphate buffer was prepared by adjusting the pH of 0.001 M potassium dihydrogen phosphate with phosphoric acid to 2. The flow rate was 1.5 ml/min. Chromatographic detection was set at 215 nm using a UV detector. The injection volume was 50 µl.

2.3. pH measurement

Powdered tablets equivalent to 40 mg enalapril maleate were dispersed in 10 ml of distilled water and the pH was measured using a Jenway 3030 pH meter.

2.4. Kinetics studies

Phosphate buffer solution of 0.010 M was prepared and sodium chloride was added to adjust the ionic strength of the buffer solution to 0.20 M. The pH of the buffer solutions was adjusted to the desired values (2.2–10.5) by the addition of aqueous sodium hydroxide solution. Samples of enalapril maleate (100 mg each) were dissolved in 250 ml of the phosphate buffers. The samples were kept in an incubator at 80°C for different storage intervals after which they have been withdrawn from the incubator and analyzed by the HPLC method.

2.5. Degradation of enalapril maleate and tablet formulations in solid matrices

2.5.1. Degradation under stress conditions

Samples of enalapril maleate powder (100 mg each), mixtures of enalapril maleate powder (100 mg each) and different formulation excipients including sodium bicarbonate, magnesium stearate and triglyceride palmitic acid were separately mixed and compressed using IR disc compressor (10 tons). The samples were placed in 100 ml quick fitted flasks, 0.1 ml of water was added to create high degree of humidity, and they were exposed to 100°C for 2 h. The samples were then

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dispersed in 100 ml of phosphate buffer of pH 2 in the cases of enalapril maleate alone and mixtures of enalapril maleate–sodium bicarbonate, and in 100 ml of ethanol when enalapril maleate was mixed with triglyceride palmitic acid or magnesium stearate. The samples were then sonicated and centrifuged when necessary. Further dilution was made to obtain solutions having concentrations of about 40 mg enalapril maleate per 100 ml before analyzing them by the HPLC method.

2.5.2. Degradation under mild conditions

Samples of enalapril maleate powder (1.0 g each) were kept in open containers incubated at 40°C under dry and 75% RH (saturated solution of lead nitrate was employed to obtain the required range of humidity) conditions for a period of 6 months. Samples of about 80 mg were then withdrawn and dissolved in 200 ml phosphate buffer of pH 2.0 in order to get solutions having about 40 mg of enalapril maleate per 100 ml. The samples were then analyzed by the HPLC method.

Samples of blistered and nonblistered tablets of product A and product B were kept at 40°C under dry and 75% RH conditions for 6 months. Each sample of the two products was then treated and analyzed as above.

2.6. Photolysis studies

Samples of enalapril maleate powder (100 mg each) and powdered enalapril maleate tablets (equivalent to 100 mg enalapril maleate) were placed in quick fitted pyrex flasks and exposed to daylight or low intensity UV light for 15 days. The samples were then diluted with the mobile phase to obtain solutions having concentrations of about 20 mg enalapril maleate per 100 ml and analyzed by HPLC.

Another set of samples of enalapril maleate powder (100 mg each) were placed in 100 ml quick fitted pyrex flasks, 50 ml of distilled water (pH 2.3) or sodium bicarbonate solution (pH 6.5) were added to each flask. The flasks were then exposed to light and the resultant solutions were analyzed by HPLC after a suitable dilution to obtain solutions having concentrations of 20 mg enalapril maleate per 100 ml of mobile phase.

3. Results and discussion

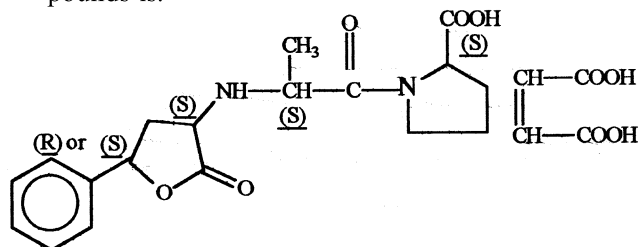
3.1. Validation of the HPLC method

Enalapril maleate and its degradation products were determined by HPLC according to the USP method [10]. The validity of the method was checked by running chromatograms for enalapril maleate and the known degradation products under the experimental set by the USP method given in the Section 2.

3.1.1. Specificity and stability indication tests of the HPLC method

Chromatograms were recorded for samples of enalapril maleate alone and after spiking with the expected impurities. The relative retention times recorded for enalapril maleate and the degradation products, enalaprilat and diketopiperazine, were 1.0, 0.30, 1.30, respectively. The photolysis and the oxidation (oxidation by H_2O_2) products of enalapril maleate were also separated well and appeared at relative retention times of 0.24 and 0.80, respectively.

Furthermore, it was possible to separate two synthesis impurities, namely, enalapril–lactone I and enalapril–lactone II which appeared at relative retention times of 0.45 and 0.52, respectively. These impurities could be formed as by-products resulting from the incomplete hydrogenation of the oxo-enalapril intermediate during the synthesis process. These enalapril–lactones were identified as, (5S)-N-(5-phenyl-dihydro-2(3H)-furanone-3(S)-yl)-L-alanyl-L-proline maleate (enalapril–lactone I) and (5R)-N-(5-phenyl-dihydro-2(3H)-furanone-3(S)-yl)-L-alanyl-L-proline maleate (enalapril–lactone II). The structural formula for these two compounds is:



Enalapril-lactone I (S) and Enalapril-lactone II (R)

The separation of all these impurities by the

ALK_ENPL_00258684

HPLC method using a UV detector set at 215 nm assures the specificity of the method for enalapril maleate and all possible impurities.

To assess the HPLC method as a stability indicator for enalapril maleate, chromatograms were recorded for enalapril maleate in different matrices under various stress conditions where degradation was stimulated by heat, light or hydrogen peroxide (Table 1). Table 1 shows a decrease in the assay of enalapril maleate under different degradation conditions associated with the formation of degradation products. These results indicate the possibility of simultaneous detection of the degradation products resulted from hydrolysis in basic media, cyclization in acidic media, photolysis or oxidation, thus the method is a stability indicator for enalapril maleate.

3.1.2. Linearity, accuracy, repeatability and intermediate precision

Calibration graphs were plotted for certain concentration ranges of enalapril maleate and its possible degradation products in pure or drug-matrix solutions. The concentration range of enalapril maleate was about 50–400 $\mu\text{g ml}^{-1}$ and that of diketopiperazine and enalaprilat was about 0.4–5 $\mu\text{g ml}^{-1}$. All calibration plots showed excellent linear-

ity with correlation coefficients of better than 0.9999. The limit of detection, LOD, and limit of quantification, LOQ, for enalapril maleate in the pure solutions were 2.0 and 6.6 $\mu\text{g ml}^{-1}$, respectively, and in drug-matrix solutions were 3.1 and 10.4 $\mu\text{g ml}^{-1}$, respectively. However, in drug-matrix solutions, LOD and LOQ for diketopiperazine were respectively, 0.068 and 0.23 $\mu\text{g ml}^{-1}$, meanwhile they were 0.019 and 0.063 $\mu\text{g ml}^{-1}$ for enalaprilat.

The accuracy of the method towards enalapril maleate was checked by analyzing various samples of enalapril maleate in the drug-matrix solutions using different concentrations covering a range of about 50–400 $\mu\text{g enalapril maleate ml}^{-1}$ (25–200% of the target concentration that is 200 $\mu\text{g ml}^{-1}$). The percent recovery was in the range of 99.1–100.5 with a bias of -0.9 to $+0.2$. The overall percent recovery was 99.7 with a relative standard deviation of 0.66%. The overall percent recoveries of diketopiperazine and enalaprilat in the drug matrix solutions were 97.4 and 103.8 with relative standard deviations of 0.67 and 1.2%, respectively.

Various samples of enalapril maleate in the drug-matrix solutions were analyzed by three analysts as a means to test the repeatability and intermediate precision of the method. The percent

Table 1

Degradation of enalapril maleate alone and with drug-excipients when stored for various storage intervals under different stress conditions in solid matrices and high humidity or in solution

Material/storage conditions	% Enalapril recovered	% Degradation		
		Diketopiperazine	Enalaprilat	Others
Enalapril maleate (disc)/100°C/2 h	77.2	21.0	2.6	–
Enalapril maleate and triglyceride palmitic acid (disc)/100°C/2 h	77.0	21.0	2.6	–
Enalapril maleate and magnesium stearate (disc)/100°C/2 h	50.0	18.0	21.0	–
Enalapril maleate and sodium bicarbonate (disc)/100°C/2 h	80.7	0.1	14.9	–
Enalapril maleate in phosphate buffer solution, pH 10.5/80°C/2 h	65.7	–	28.0	–
Enalapril maleate in phosphate buffer solution, pH 2.2/80°C/24 h	83.5	10.0	–	–
Enalapril maleate in water solution (pH 2.3)/daylight/room temperature/15 days	97.5	–	–	5.0 (photolysis product)
Enalapril maleate in 3.5% H_2O_2 solution/65°C/12 h	66.0	3.0	–	5.0 (oxidation product)

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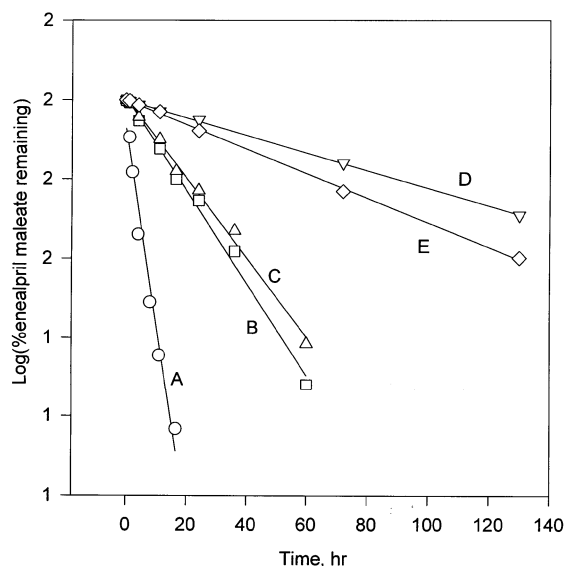


Fig. 1. Plots of log (% enalapril maleate remaining) against time for the degradation of enalapril maleate in samples of about $400 \mu\text{g ml}^{-1}$ enalapril maleate in aqueous buffers of pH 10.5 (A); 7.0 (B); 5.5 (C); 3.4 (D); and 2.2 (E) at 80°C .

recoveries for enalapril maleate obtained by the analysts was in the range of 100.0–101.8 and the relative standard deviation (R.S.D.) was in the range of 0.1–0.9%. However, the overall percent recovery obtained by the three analysts for enalapril maleate was 101.1 and R.S.D. was 0.57%.

3.2. Kinetics of enalapril maleate degradation

The stability of enalapril maleate was investigated in aqueous matrix containing 0.010 M phosphate buffer of pH values of 10.5, 7.0, 5.5, 3.4 and 2.2 with ionic strength adjusted to 0.2 M and stored at 80°C . Enalapril maleate left after various storage intervals was assessed by the stability indicating HPLC method mentioned above. The linearity of the plots of log (% enalapril maleate) remaining against time (Fig. 1) indicates that the degradation follows a first-order kinetics. Since water and other matrix components are in large excess to enalapril maleate, the kinetics would be a typical pseudo first-order process. Fig. 1 shows that the rate of enalapril loss is depen-

dent upon the solution pH and it is obvious that the degradation at pH 10.5 is more significant than that at lower pH values. This kinetic behavior is compatible with the earlier reports for enalapril maleate [2] and the *N*-carboxyl dipeptide angiotensin converting enzyme inhibitors [3–7].

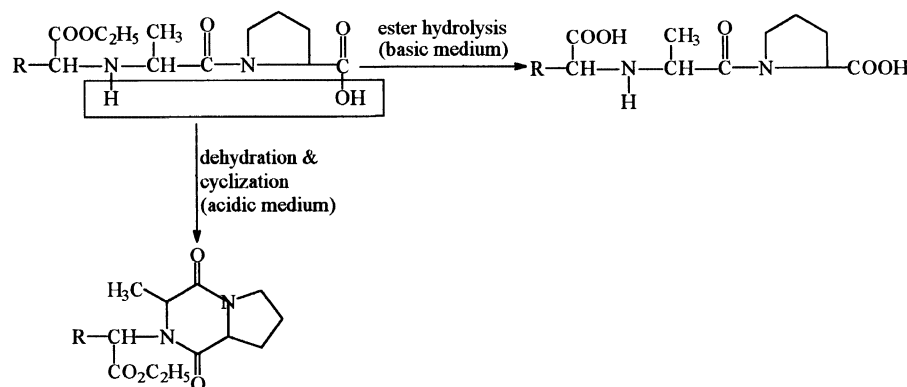
3.3. Degradation of enalapril maleate in solid formulations

The stability and pathway of degradation of enalapril maleate alone or in the presence of possible drug-excipients in solid matrices were first investigated under stress conditions where the components were kept for 2 h under a temperature of 100°C and relative humidity of $>90\%$. Table 1 shows that enalapril maleate alone or in the presence of triglyceride palmitic acid drug-excipient decomposes mainly into diketopiperazine (21.0%) with a small proportion of enalaprilat (2.6%). However, the main degradation product in the presence of sodium bicarbonate is enalaprilat (14.9%) with insignificant proportion of diketopiperazine (0.1%). Enalapril maleate in the presence of magnesium stearate showed, significantly, a higher degree of degradation with almost similar proportions of diketopiperazine (18.0%) and enalaprilat (21%) degradation products (Table 1).

It is obvious from the above results that the degree and pathway of degradation of enalapril maleate are dependent upon humidity and the pH of the drug-matrix. This degradation may be ascribed to the drug-matrix interaction in the solid form at elevated temperatures in the presence of moisture. The pathway of degradation has been attributed to the dehydration followed by intramolecular cyclization in the acidic medium, which leads to the formation of diketopiperazine and to the ester hydrolysis of enalapril maleate that leads to the formation of enalaprilat in the basic medium [1,2]. Scheme 1 below, represents these two reactions.

Enalapril maleate powder stored for 6 months at 40°C in the absence and presence of humidity showed insignificant degradation; 0.1–0.2% of diketopiperazine and 0.1% of enalaprilat were detected (Fig. 2, chromatogram A and Table 2).

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Scheme 1. Degradation of enalapril maleate in acidic and basic media.

Thus, the mild temperature, humidity and moderate pH values for the drug-matrix do not effect the degradation of enalapril maleate.

When nonblistered tablets of product A and product B were kept at 40°C and 75% RH for 6 months, a degradation to diketopiperazine and enalaprilat has been detected by the HPLC chromatograms; this degradation was relatively more significant for product A compared with product B; 85.3 and 97.4% of enalapril have been recovered from samples of product A and product B, respectively, (Table 2 and Fig. 2, chromatogram B). Infact, enalaprilat was the main degradant (11.9%) from product A and diketopiperazine was the main degradant (5.7%) from product B.

Blistered tablets of product B showed an insignificant degradation (Table 2) when stored at 40°C under dry (a recovery of 101.5% enalapril with a total degradation of 1.4%) and 75% RH (a recovery of 101.2% enalapril with a total degradation of 1.3%). Meanwhile, blistered tablets of product A under the same conditions showed a relatively more tendency for degradation when stored at 40°C under dry (a recovery of 97.8% enalapril) and 75% RH (a recovery of 95.0% enalapril) conditions with a total degradation of 3.5 and 4.4%, respectively.

It is obvious from the above results that the degree and pathway of degradation of the tablet formulations are similar to those for enalapril maleate under the stress conditions mentioned above and they are dependent on the pH of the

drug-matrix, temperature and humidity. The product with an acidic matrix showed a less significant degradation compared with that with a basic matrix when both were stored under the same conditions. Furthermore, blistering of the tablets in both formulations reduces the degradation significantly even in the presence of 75% RH.

3.4. Photolysis of enalapril maleate alone and in its tablet formulations

Photolysis of enalapril maleate as powder or in aqueous acidic or basic solution and in tablet formulations (products A and B) was investigated by exposing them to the daylight and low intensity UV light for 15 days. HPLC chromatograms for enalapril maleate alone or in acidic (pH 2.3) aqueous solutions when exposed to daylight or to low intensity UV light, showed new peak at a retention time of about 1.9 min in addition to those for enalapril, diketopiperazine and enalaprilat (Fig. 3). It was not possible to quantify this peak accurately since the photodegradation product is unknown. Thus, the quantity of this product was estimated based on its relative peak areas in the HPLC chromatograms. The estimation for the photodegradation product indicated that enalapril maleate alone had a significant photodegradation (3.3% for the dry powder and 5.0% for the aqueous solution of pH 2.3, Table 3) when exposed to daylight. The photolysis degradation was negligible in the basic solutions of pH

ALK_ENPL_00258687

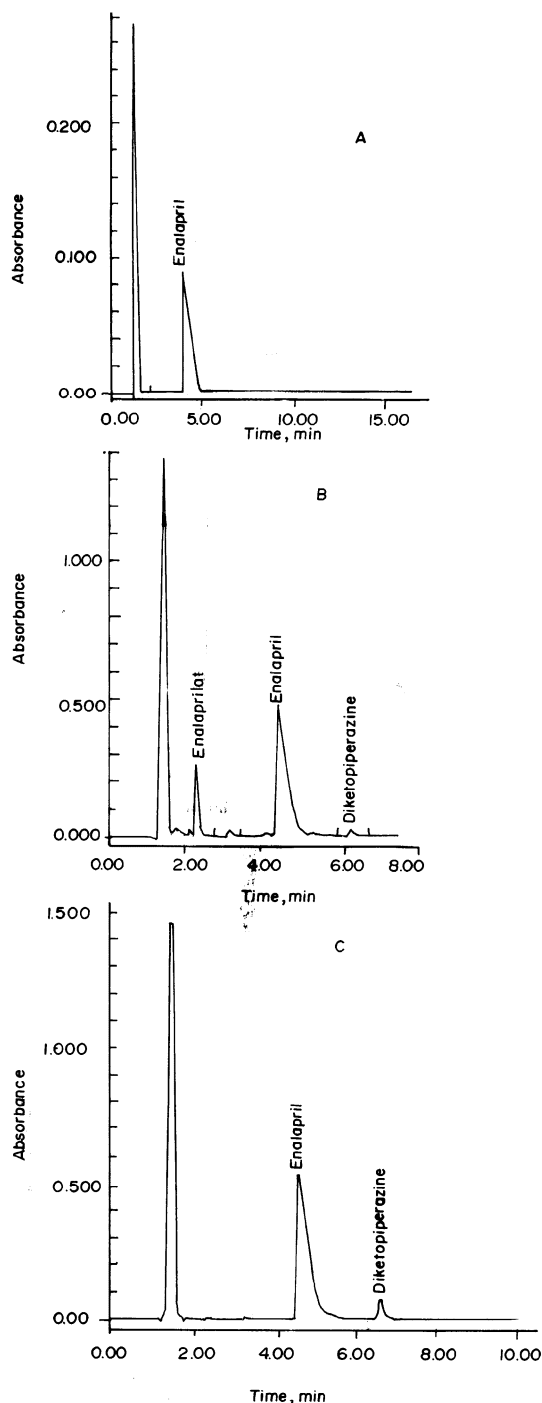


Fig. 2. HPLC chromatograms for enalapril maleate alone (chromatogram A), tablets of product A (chromatogram B) and tablets of product B (chromatogram C) after storage at 40°C and 75% RH for 6 months.

6.5 (Table 3). Also, under UV light the photolysis of enalapril maleate in powder or in basic solutions was insignificant (0.2% for the dry powder, Table 3).

The photodegradation peak had appeared in the chromatograms of product B (Fig. 3, chromatogram C) after exposure to daylight although its contribution to the total area was relatively insignificant (0.9%, Table 3). However, chromatograms of product A showed an insignificant photolysis (traces, Fig. 3, chromatogram B, Table 3). The reduction in the photodegradation of product B with an acidic drug-matrix in comparison to enalapril maleate powder may be ascribed to the decrease in the surface area exposed to light in the presence of formulation excipients. On the other hand, the better light stability showed by product A might be ascribed to the basicity of the drug-matrix and/or the presence of red and yellow iron oxide.

4. Conclusion

The degradation of enalapril maleate can be studied by an HPLC stability indicating method. Enalapril maleate powder is stable against moderate heat and humidity; 40°C and 75% RH. However, in tablet formulations, enalapril maleate would show some instability, which may be ascribed to its interaction with the drug-matrix. The major degradation kinetics of enalapril maleate was observed to be a pseudo first order.

Enalapril maleate tablet formulations with an acidic matrix would have a better stability against temperature and humidity over those formulations comprising a basic matrix. Humidity, type of the drug-matrix and its pH and blistering of the tablets may be the major factors that affect the stability of the drug in its tablet formulations. Enalapril maleate in the tablets with a basic matrix may have a relatively improved stability against light compared with the tablets of the acidic matrix.

Consequently, enalapril maleate tablet formulations with basic matrices should not be exposed to high temperature and moisture due to its instability under these conditions, meanwhile, the formu-

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Table 2

Stability of enalapril maleate powder alone and in tablet formulations stored for 6 months at 40°C under dry and humid conditions

Material	Storage conditions	% Enalapril recovered	% Degradation	
			Diketopiperazine	Enalaprilat
Enalapril maleate powder	Dry	100.0	0.1	0.1
Enalapril maleate powder	75% RH	100.0	0.2	0.1
Product A (nonblistered tablets)	75% RH	85.3	1.3	11.9
Product B (nonblistered tablets)	75% RH	97.4	5.7	0.3
Product A (blistered tablets)	Dry	97.8	2.7	0.8
Product A (blistered tablets)	75% RH	95.0	3.2	1.2
Product B (blistered tablets)	Dry	101.5	1.2	0.2
Product B (blistered tablets)	75% RH	101.2	1.0	0.3

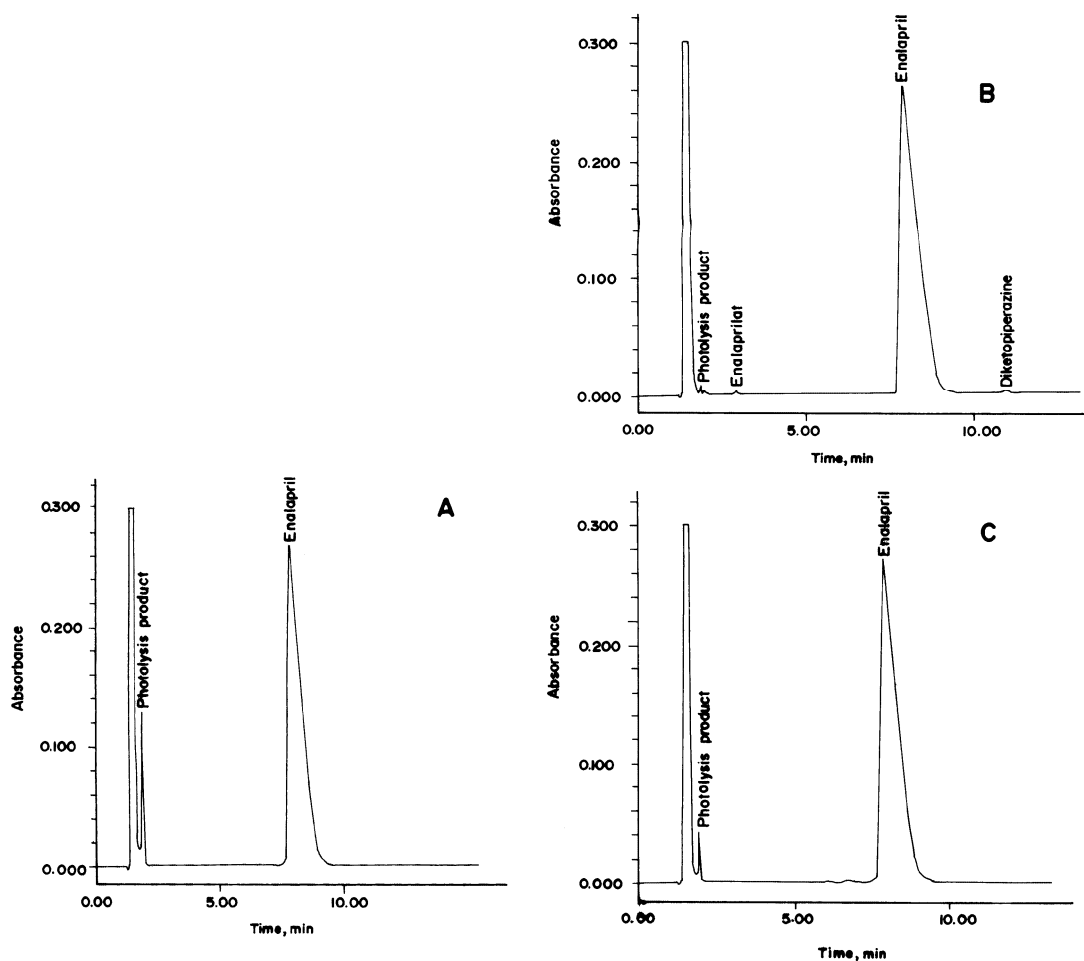


Fig. 3. HPLC chromatograms for enalapril maleate powder (chromatogram A), tablets of product A (chromatogram B) and tablets of product B (chromatogram C) after storage at room temperature exposed to daylight for 15 days.

ALK_ENPL_00258689

Table 3

Photolysis of enalapril maleate as dry powder alone, in tablet formulations and in aqueous solutions after exposure to daylight and low intensity UV light for 15 days^a

Sample	Storage condition	% Enalapril recovered	% Degradation		
			DKP	EA	PD
Enalapril maleate	Dark	99.6	–	–	–
Enalapril maleate	Daylight	99.5	–	–	3.3
Enalapril maleate	UV light	99.8	–	–	0.2
Product B	Dark	103.0	–	–	–
Product B	Daylight	102.7	–	–	0.9
Product B	UV light	103.3	–	–	0.2
Product A	Dark	100.6	0.7	0.3	–
Product A	Daylight	97.7	0.5	0.3	Traces
Product A	UV light	97.8	0.7	0.3	Traces
Enalapril maleate	Aqueous solution (pH 2.3)/dark	99.4	0.4	0.5	–
Enalapril maleate	Aqueous solution(pH 2.3)/daylight	97.5	–	–	5.0
Enalapril maleate	Aqueous solution (pH 2.3)/UV light	100.0	0.4	0.6	–
Enalapril maleate	Aqueous solution+ NaHCO ₃ (pH 6.5)/dark	86.0	–	13.2	–
Enalapril maleate	Aqueous solution+ NaHCO ₃ (pH 6.5)/daylight	90.5	–	8.1	Traces
Enalapril maleate	Aqueous solution+ NaHCO ₃ (pH 6.5)/UV light	82.0	–	16.2	–

^a EA: enalaprilat; DKP: diketopiperazine; PD: photodegradation product.

lations with acidic matrices should be protected from light.

Acknowledgements

JPM and KFUPM are thanked for the support of this research project.

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Exhibit 8

Constantinides, P.

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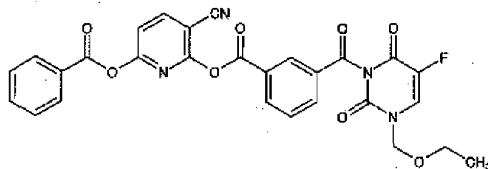
Dihydrochloride, $C_{29}H_{40}N_2O_4 \cdot 2HCl$, *emetine hydrochloride*, *Hemometina*. Contains water of crystallization varying from 3 to 8 H_2O . Clusters of needles after drying at 105° , mp $235-255^\circ$ (dec). $[\alpha]_D^{25} +11^\circ$ ($c = 1$) to $[\alpha]_D^{25} +21^\circ$ ($c = 8$), calculated for the anhydrous salt. One gram of the hydrated salt dissolves in about 7 ml water. pH of aq soln (1 g in 50 ml) 5.6. Sol in alcohol. Solid and solutions turn yellow on exposure to light or heat. LD_{50} (calculated as base) in mice (mg/kg): 32 s.c.; 30 orally (Child).

Acetarsone salt, *Arsemétine*.

THERAP CAT: Antiamoebic.

THERAP CAT (VET): Hydrochloride has been used as an antiamoebic and in lung worm infection.

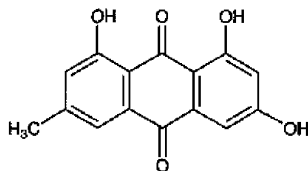
3601. Emitefur. 3-[[3-(Ethoxymethyl)-5-fluoro-3,6-dihydro-2,6-dioxo-1(2H)-pyrimidinyl]carbonyl]benzoic acid 6-(benzoyloxy)-3-cyano-2-pyridinyl ester; 3-[[3-(6-benzoyloxy-3-cyano-2-pyridyl)oxycarbonyl]benzoyl]-1-(ethoxymethyl)-5-fluorouracil; BOF-A2. $C_{28}H_{19}FN_3O_8$; mol wt 558.48. C 60.22%, H 3.43%, F 3.40%, N 10.03%, O 22.92%. Bifunctional prodrug composed of a derivative of 5-fluorouracil (5-FU) and 3-cyano-2,6-dihydroxypyridine (CNDP), an inhibitor of 5-FU degradation by dihydrouracil dehydrogenase. Prepn: S. Fujii, Ger. pat. 3,709,699; *idem*, U.S. pat. 4,983,609 (1988, 1991 both to Otsuka); M. Hirohashi *et al.*, *Chem. Pharm. Bull.* **41**, 1498 (1993). Antitumor activity: S. Fujii *et al.*, *Japan. J. Cancer Res.* **80**, 173 (1989). Mechanism of action: T. Okayasu *et al.*, *ibid.* **85**, 101 (1994). Clinical evaluation in lung cancer: Y. Nakai *et al.*, *Acta Oncol.* **33**, 523 (1994). Toxicity study: H. Kinoshita *et al.*, *Yakuri to Chiryō* **22**, 81 (1994), *C.A.* **121**, 99197 (1994).



Crystals, mp $162-164^\circ$. LD_{50} in mice, male rats, female rats (mg/kg): > 5000, 1850, 1934 orally (Kiroshita).

THERAP CAT: Antineoplastic.

3602. Emodin. 1,3,8-Trihydroxy-6-methyl-9,10-anthracenedione; 1,3,8-trihydroxy-6-methylanthraquinone; 4,5,7-trihydroxy-2-methylanthraquinone; frangula emodin; rheum emodin; archin; frangulic acid. $C_{15}H_{10}O_5$; mol wt 270.24. C 66.67%, H 3.73%, O 29.60%. Occurs mostly as the rhamnoside (see Frangulin) in rhubarb root, in alder buckthorn (*Rhamnus frangula* L.), in *Cascara sagrada* (*Rhamnus purshiana* DC., *Rhamnaceae*), also in *Rumex* and in other *Polygonaceae*. Isolin from rhubarb root: Tutin, Clewer, *J. Chem. Soc.* **99**, 946 (1911); Carelli, Giuliano, *Farmaco Ed. Prat.* **12**, 184 (1957); from bark of alder buckthorn: Bridel, Charaux, *Bull. Soc. Chim. Biol.* **15**, 648 (1933). Identity with archin: Chaudhry *et al.*, *J. Sci. Ind. Res. (India)* **9B**, No. 6, 142 (1950), *C.A.* **44**, 9396h (1950). Synthesis from 3,5-dinitrophthalic anhydride and *m*-cresol: Elder, Widmer, *Helv. Chim. Acta* **6**, 966 (1923); from 2-methylanthraquinone: Ayyangar *et al.*, *J. Sci. Ind. Res. (India)* **20B**, 493 (1961), *C.A.* **57**, 8514b (1962).

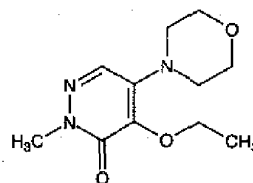


Orange needles from alc or by sublimation at 12 mm. mp $256-257^\circ$. Absorption max (ethanol): 222, 252, 265, 289, 437 nm ($\log \epsilon$ 4.55, 4.26, 4.27, 4.34, 4.10). Practically insol in water; sol in alc, aq alkali hydroxide solns (cherry-red color), Na_2CO_3 and NH_3 solns. Soly at 25° (g/100 ml of satd soln): ether 0.140; chloroform 0.071; carbon tetrachloride 0.010; carbon bisulfide 0.009; benzene 0.041.

3-Methyl ether, $C_{16}H_{12}O_5$, 1,8-dihydroxy-3-methoxy-6-methylanthraquinone, *rheochrysidin*. Brick-red, monoclinic needles, mp 207° . Occurs naturally as *physcione* or *parietin*. Trimethyl ether, $C_{18}H_{16}O_5$, pale yellow needles, mp 225° . Note: See also Aloe-emodin.

THERAP CAT: Cathartic.

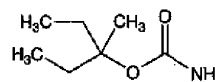
3603. Emorfazone. 4-Ethoxy-2-methyl-5-(4-morpholinyl)-3(2H)-pyridazinone; M-73101; Nandron; Pentoyl. $C_{17}H_{17}N_3O_3$; mol wt 239.27. C 55.22%, H 7.16%, N 17.56%, O 20.06%. Prepn: K. Satoda *et al.*, *Japan. pat.* **72** 24,030 (1972 to Morishita), *C.A.* **77**, 164732f (1972); M. Takaya *et al.*, *J. Med. Chem.* **22**, 53 (1979). Metabolism studies: T. Hayashi *et al.*, *Chem. Pharm. Bull.* **26**, 3124 (1978); **27**, 317 (1979). General pharmacological study: M. Sato *et al.*, *Nippon Yakurigaku Zasshi* **75**, 291 (1979), *C.A.* **91**, 117292 (1979). Mechanism of action studies: M. Sato, A. Yamaguchi, *Arzneimittel-Forsch.* **32**, 379 (1982). Antigenicity study: M. Sato *et al.*, *Oyo Yakuri* **18**, 65 (1979), *C.A.* **92**, 104391 (1980). Toxicity studies: *idem*, *ibid.* **16**, 1011 (1978), *C.A.* **90**, 197741 (1979); C. Onodera *et al.*, *J. Toxicol. Sci.* **4**, 229 (1979); K. Shimpo *et al.*, *ibid.* **255**.



Cryst from methanol/isopropyl ether, mp $89-91^\circ$. LD_{50} i.p. in mice: 700 mg/kg (Takaya).

THERAP CAT: Anti-inflammatory; analgesic.

3604. Emlycamate. 3-Methyl-3-pentanol carbamate; 1-ethyl-1-methylpropyl carbamate; diethyl methyl carbinol urethan; 3-methyl-3-pentyl carbamate; methyl diethyl carbinol urethan; *tert*-hexanol carbamate; Kabi 925; JD-91; Nuncital; Restetal; Statran; Striatran. $C_9H_{19}NO_2$; mol wt 145.20. C 57.90%, H 10.41%, N 9.65%, O 22.04%. Prepn: Ger. pat. **245,491** (1912 to Chinifabr. Zimmer); Ger. pat. **254,472** (1912 to E. Merck); Melander, Hanshoff, U.S. pat. **2,972,564** (1961 to Kabi).



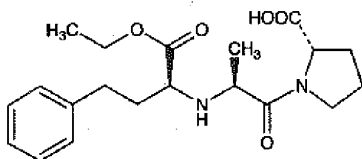
Needles from 30% ethanol, mp $56-58.5^\circ$. bp_{10} 35° ; bp_{97} 24° . Slight odor of camphor. Soly in water: 4.0 mg/ml. Freely sol in alcohol, ether, benzene, glycol ethers.

THERAP CAT: Anxiolytic.

3605. Enalapril. (S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline; 1-[N-[(S)-1-carboxy-3-phenylpropyl]-L-alanyl]-L-proline 1'-ethyl ester. $C_{20}H_{28}N_2O_5$; mol wt 376.45. C 63.81%, H 7.50%, N 7.44%, O 21.25%. Angiotensin-converting enzyme (ACE) inhibitor; de-esterified *in vivo* to its active diacid metabolite, enalaprilat, *q.v.* Prepn: A. A. Patchett *et al.*, *Nature* **288**, 280 (1980); *idem*, *Eur. pat. Appl.* **12,401**; E. E. Harris *et al.*, U.S. pat. **4,374,829** (1980, 1983 both to Merck & Co.). Pharmacology: D. M. Gross *et al.*, *J. Pharmacol. Exp. Ther.* **216**, 552 (1981); C. S. Sweet *et al.*, *ibid.* **558**. Bioavailability and metabolism: E. H. Ulm, *Drug Metab. Rev.* **14**, 99 (1983). Comprehensive description: D. P. Ip, G. S. Brenner, *Anal. Profiles Drug Subs.* **16**, 207-243 (1987). Clinical trial in congestive heart failure: Consensus Trial Study Group, *N. Engl. J. Med.* **316**, 1429 (1987). Review of clinical experience in hypertension: H. J. Gomez *et al.*, *J. Cardiovasc. Pharmacol.* **15**, Suppl. 3, S26-S29 (1990); of clinical pharmacokinetics: R. J. MacFadyen *et al.*, *Clin. Pharmacokinet.* **25**, 274-282 (1993); of combination with hydrochlorothiazide: P. L. Malini, *Adv. Ther.* **10**, 253-262 (1993).

Enciprazine

3610



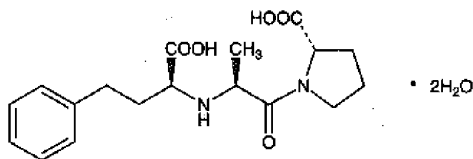
Maleate, $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, MK-421, Amprace, Bitensil, Cardiovet, Enacard, Enaloc, Enapren, Glioten, Hipoartel, Innovace, Lotrial, Olivin, Pres, Renitec, Reniten, Renivace, Vasotec, Xanef. White to off-white crystalline powder, mp 143-144.5°. Soly (g/ml): water 0.025; alcohol 0.08; methanol 0.20. $[\alpha]_D^{25} -42.2^\circ$ ($c = 1$ in methanol). pH (1% water) 2.6. pK_{a1} 3.0; pK_{a2} (25°) 5.4.

Mixture of maleate with hydrochlorothiazide, Acesistem, Co-Renitec, Innovide, Renacor, Vasoretic, Xynertec.

THERAP CAT: Antihypertensive.

THERAP CAT (VET): In treatment of heart failure in dogs.

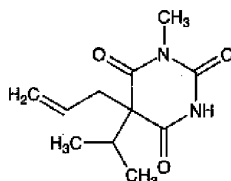
3606. Enalaprilat. (S)-1-[N-(1-Carboxy-3-phenylpropyl)-L-alanyl]-L-proline dihydrate; enalaprilic acid; MK-422; Vasotec IV. $C_{18}H_{24}N_2O_5 \cdot 2H_2O$; mol wt 384.43. C 56.24%, H 7.34%, N 7.29%, O 29.13%. Nonsulfhydryl dipeptide angiotensin converting enzyme (ACE) inhibitor. Prepn: A. A. Patchett *et al.*, *Nature* **288**, 280 (1980); *idem*, *Eur. pat. Appl.* 12,401; E. E. Harris *et al.*, U.S. pat. 4,374,829 (1980, 1983 both to Merck & Co.). Active metabolite of enalapril, q.v.: D. J. Tocco *et al.*, *Drug Metab. Dispos.* **10**, 15 (1982). Pharmacology: D. M. Gross *et al.*, *J. Pharmacol. Exp. Ther.* **216**, 552 (1981); M. A. Nelson *et al.*, *Clin. Exp. Pharmacol. Physiol. Suppl.* **7**, 87 (1982); T. A. Unger *et al.*, *Biochem. Pharmacol.* **31**, 3063 (1982). Bioavailability: M. L. Cohen *et al.*, *J. Pharmacol. Exp. Ther.* **226**, 192 (1983). Kinetics of enzyme inhibition: C. H. Reynolds, *Biochem. Pharmacol.* **33**, 1273 (1984). Pharmacokinetics: K. S. Pang *et al.*, *Drug Metab. Dispos.* **12**, 309 (1984). Acute hemodynamic effects in essential hypertension: A. C. Simon *et al.*, *Clin. Pharm. Ther.* **43**, 49 (1988). Clinical evaluation in severe and malignant hypertension: D. J. DiPette *et al.*, *ibid.* **38**, 199 (1985).



Needles from H_2O , mp 148-151°. $[\alpha]_D -67.0^\circ$ (0.1M HCl).

THERAP CAT: Antihypertensive.

3607. Enallylpropymal. 1-Methyl-5-(1-methylethyl)-5-(2-propenyl)-2,4,6-(1H,3H,5H)-pyrimidinetrione; 5-allyl-5-isopropyl-1-methylbarbituric acid; N-methyl-5-allyl-5-isopropylbarbituric acid. $C_{11}H_{16}N_2O_3$; mol wt 224.26. C 58.91%, H 7.19%, N 12.49%, O 21.40%. Prepn: Schneider, U.S. pat. 2,072,829 and Brit. pat. 454,779 (1937, 1936, both to Hoffmann-La Roche).



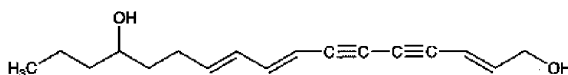
Crystals, mp 56-57°. bp_{12} 176-178°. Soluble in organic solvents.

Sodium salt, $C_{11}H_{15}N_2NaO_3$, Narconumal. Sol in water.

Caution: May be habit forming. This is a controlled substance (depressant) listed in the U.S. Code of Federal Regulations, Title 21 Parts 329.1 and 1308.13 (1995).

THERAP CAT: Sedative, hypnotic.

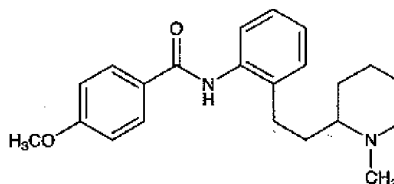
3608. Enanthotoxin. (E,E,E)-2,8,10-Heptadecatriene-4,6-diene-1,14-diol; oenanthotoxin. $C_{17}H_{22}O_2$; mol wt 258.36. C 79.03%, H 8.58%, O 12.39%. The poisonous principle of *Oenanthe crocata* L., *Umbelliferae*, the hemlock water dropwort, a toxic plant known since 1746 and believed to be the most poisonous plant in England. Isoln: Clarke *et al.*, *J. Pharm. Pharmacol.* **1**, 377 (1949). Structure studies: Anet *et al.*, *Chem. & Ind. (London)* **1952**, 757; *J. Chem. Soc.* **1953**, 309. Synthesis of DL-form: Bohlmann, Viehe, *Ber.* **88**, 1245 (1955). Fluorimetric determ: B. Del Castillo *et al.*, *Ital. J. Biochem.* **29**, 233 (1980). Blocking of sodium current and intramembrane charge movement: J. M. Dubois, M. F. Schneider, *Nature* **289**, 685 (1981); *idem*, *Toxicol.* **20**, 49 (1982). Toxicity study: M. P. Martinez-Honduvilla *et al.*, *Arch. Pharmacol. Toxicol.* **7**, 197 (1981).



Large prisms (natural) or star-shaped crystals (synthetic). Unstable, dec by light and air to brown insol resin. mp 87° (natural), 68° (synthetic). $[\alpha]_D^{25} +30.5^\circ$ ($c = 2.0$ in methanol). uv max: 213, 252, 267, 281, 296, 315.5, 337.5 ($\epsilon \times 10^{-3}$ 17.5, 33, 29, 17.5, 30.5, 40, 29). Practically insol in water, petr ether, alkalies, dil mineral acids. Readily sol in chloroform, ethanol, methanol, ether, benzene. Average LD i.p. in mice: 0.83 mg/kg (Clarke). LD₅₀ i.p. in rats: 2.94 mg/kg (Martinez-Honduvilla).

Caution: Very toxic. May cause convulsions, death.

3609. Encainide. (±)-4-Methoxy-N-[2-[2-(1-methyl-2-piperidinyl)ethyl]phenyl]benzamide; (±)-2'-[2-(1-methyl-2-piperidinyl)ethyl]-p-anisilide; 4-methoxy-2'-[2-(1-methyl-2-piperidinyl)ethyl]benzanilide. $C_{22}H_{28}N_2O_2$; mol wt 352.48. C 74.97%, H 8.01%, N 7.95%, O 9.08%. Anti-arrhythmic benzanilide derivative. Prepn: S. J. Dykstra, J. L. Minielli, *Ger. pat.* 2,210,154 (1972 to Bristol-Myers), C.A. **78**, 4138j (1973); *idem*, U.S. pat. 3,931,195 (1976 to Mead Johnson); S. J. Dykstra *et al.*, *J. Med. Chem.* **16**, 1015 (1973). Anti-arrhythmic pharmacology in animals: J. E. Byrne *et al.*, *J. Pharmacol. Exp. Ther.* **200**, 147 (1977). Clinical pharmacology and efficacy in chronic ventricular arrhythmia: D. M. Roden *et al.*, *N. Engl. J. Med.* **302**, 877 (1980). Electrophysiology and effects on cardiac conduction: M. Sami *et al.*, *Am. J. Cardiol.* **44**, 526 (1979). Hemodynamic effects: M. Sami *et al.*, *ibid.* **52**, 507 (1983). Adverse effects: R. A. Winkle *et al.*, *Am. Heart J.* **102**, 857 (1981). Comparison with other Class I anti-arrhythmic agents: A. Pottage, *Am. J. Cardiol.* **52**, 24C (1983). Series of articles on pharmacology, pharmacokinetics, metabolism, clinical safety and efficacy: *ibid.* **58**(5), 1C-116C (1986). Review: L. B. Mitchell, R. A. Winkle in *New Drugs Annual: Cardiovascular Drugs*, vol. **1**, A. Scriabine, Ed. (Raven Press, New York, 1983) pp 93-107.



Hydrochloride, $C_{22}H_{28}N_2O_2 \cdot HCl$, MJ-9067, Enkade, Enkaid. Crystals, mp 131.5-132.5°. Freely sol in water; slightly sol in ethanol. Insol in heptane. LD₅₀ in mice, dogs (mg/kg): 86, 43 orally; 16, 17 i.v. (Mitchell, Winkle).

THERAP CAT: Antiarrhythmic (class IC).

3610. Enciprazine. (±)-4-(2-Methoxyphenyl)-α-[3,4,5-trimethoxyphenoxy)methyl]-1-piperazineethanol; (±)-1-[3-(3,4,5-trimethoxyphenoxy)-2-hydroxypropyl]-4-(2-methoxyphenyl)piperazine. $C_{23}H_{32}N_2O_6$; mol wt 432.52. C 63.87%,

Consult the Name Index before using this section.

Page 603

Curriculum Vitae

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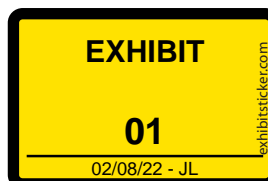
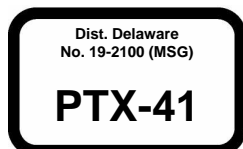
ST. JOSEPH HOSPITAL, Concordia, Kansas (1979-1981)
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Page 1 of 7

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CF Fulk, A Gayed, B Lund, GL Mosher, DO Thompson and R Wedel, Preserved formulations containing Captisol® brand of sulfobutylether- β -cyclodextrin, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

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Exhibit 7

Pradhan, M.

02/03/22

@ptus



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Book No. FDC-865 Previous Book No. — Issue Date: 11/09/2017
Name of the product: ENALAPRIL MALEATE ORAL B. No. starts with: C618-01
SOLUTION 1MG/ML
Issued To: Manoj Senapati Sign: MK Date: 11/09/2017
Issued By: T. Satyanarayana Sign: SC Date: 11/09/2017

Dist. Delaware
No. 19-2100 (MSG)

PTX-52

Index of Experiments

Product Name: *Erythrapril maleate oral solution 1mg/ml*

Sr. No.	Aim of experiment	Batch No.	Page No.	Initiation Date	Comple. Date	Prep by	Checked by
01	<i>Trial batch with saccharin</i>	<i>C618-01</i>	<i>01</i>	<i>11/09/17</i>	<i>11/09/17</i>	<i>A</i>	<i>MK</i>
02	<i>To prepare batch same as innovator formula</i>	<i>C618-02</i>	<i>2</i>	<i>11/10/17</i>	<i>11/10/17</i>	<i>A</i>	<i>MK</i>
03	<i>Replacement of sodium benzoate with methyl paraben and propyl paraben</i>	<i>C618-03</i>	<i>03</i>	<i>15/11/17</i>	<i>15/11/17</i>	<i>A</i>	<i>MK</i>
04	<i>To optimize the concentration of buffering agent with methyl paraben and propyl paraben as antimicrobial preservative</i>	<i>C618-04</i>	<i>04</i>	<i>17/11/17</i>	<i>17/11/17</i>	<i>A</i>	<i>MK</i>
05	<i>To take trial batch with methyl paraben and propyl paraben as antimicrobial preservative.</i>	<i>C618-05</i>	<i>05</i>	<i>17/11/17</i>	<i>17/11/17</i>	<i>A</i>	<i>MK</i>
06	<i>To prepare placebo for B.No. C618-05</i>	<i>C618-05P</i>	<i>06</i>	<i>17/11/17</i>	<i>17/11/17</i>	<i>A</i>	<i>MK</i>
07	<i>To prepare batch using (replacing sodium benzoate with) methyl and propyl paraben and reducing flavor concentration</i>	<i>C618-06</i>	<i>07</i>	<i>28/02/18</i>	<i>28/02/18</i>	<i>A</i>	<i>MK</i>
08	<i>To prepare placebo of B.No. C618-06</i>	<i>C618-06P</i>	<i>08</i>	<i>28/02/18</i>	<i>28/02/18</i>	<i>A</i>	<i>MK</i>
09	<i>To prepare batch similar to batch no C618-06 with replacing methyl paraben and propyl paraben with sodium methyl paraben and sodium propyl paraben</i>	<i>C618-07</i>	<i>09</i>	<i>01/03/18</i>	<i>01/03/18</i>	<i>A</i>	<i>MK</i>
10	<i>To prepare placebo of B.No. C618-07</i>	<i>C618-07P</i>	<i>10</i>	<i>05/03/18</i>	<i>05/03/18</i>	<i>A</i>	<i>MK</i>

Index of Experiments

Product Name: Enalapril maleate oral solution 1mg/ml

Sr. No.	Aim of experiment	Batch No.	Page No.	Initiation Date	Comple. Date	Prep by	Checked by
11	To prepare batch with mannitol as additional sweetener	C618-08	11	05/03/18	05/03/18	4	Mh
12	To prepare placebo for B.No. C618-08	C618-08P	12	05/03/2018	05/03/2018	4	Mh
13	To prepare Placebo for citric acid and sodium citrate (batch formula similar to B.No. C618-02)	C618-09	13	07/03/18	07/03/18	4	Mh
14	To prepare placebo for Sucralose (batch formula similar to B.No. C618-02)	C618-10	14	07/03/18	07/03/18	4	Mh
15	To prepare batch with mannitol as additional sweetener	C618-11	15	07/03/18	07/03/18	4	Mh
16	To prepare placebo for B.No. C618-11	C618-11P	16	07/03/18	07/03/18	4	Mh
17	To prepare trial batch with different pH (i.e. pH 2.7 pH 3.0 pH 3.5 pH 4.0)	C618-12A C618-12B C618-12C C618-12D	17	09/03/18	09/03/18	4	Mh
18	To prepare placebo for B.No. C618-12A C618-12B C618-12C C618-12D	C618-12AP C618-12BP C618-12CP C618-12DP	18	09/03/18	09/03/18	4	Mh
19	To prepare plain placebo solution of citric acid anhydrous, sodium citrate anhydrous and sodium benzoate	C618-13	21	12/03/18	12/03/18	4	Mh

Index of Experiments

Product Name: Enalapril maleate oral solution 1mg/ml

Sr. No.	Aim of experiment	Batch No.	Page No.	Initiation Date	Comple. Date	Prep by	Checked by
15	To prepare placebo for Citric acid anhydrous, sodium citrate anhydrous and sodium benzoate.	C618-14	22	12/03/18	12/03/18	4	Mh
16	To prepare placebo for Sodium benzoate.	C618-15	23	12/03/18	12/03/18	4	Mh
17	To take trial with increased concentration of sod. methyl paraben and sod. propyl paraben.	C618-16	24	16/03/18	16/03/18	4	Mh
18	To prepare placebo for B.No. C618-16	C618-16P	25	16/03/18	16/03/18	4	Mh
19	To take trial with formula similar to B.No. C618-16 with glycerin 1.0mg/mL	C618-17	26	16/03/18	16/03/18	4	Mh
20	To prepare placebo for B.No. C618-17	C618-17P	27	16/03/18	16/03/18	4	Mh
21	To take trial with formula similar to B.No. C618-16 with xylitol 0.1 mg/mL	C618-18	28	19/03/18	19/03/18	4	Mh
22	To prepare placebo for B.No. C618-18	C618-18P	29	19/03/18	19/03/18	4	Mh
23	To prepare trial batch with methyl paraben, propyl paraben with xylitol	C618-19	30	20/03/18	20/03/18	4	Mh
24	To prepare placebo for B.No. C618-19	C618-19P	31	20/03/18	20/03/18	4	Mh
25	Total batch for Filter Suitability Study	C618-20	32	03/04/18	03/04/18	4	Mh

Index of Experiments

Product Name: Enalapril maleate oral solution 1mg/mL

Sr. No.	Aim of experiment	Batch No.	Page No.	Initiation Date	Comple. Date	Prep by	Checked by
26	Trial batch using sodium methyl paraben and sodium propyl paraben of Gujarat organics.	C618-21	33	03/04/18	03/04/18	4	MK
29	To take trial with xylitol at concentration of 0.26 mg/mL	C618-22 C618-22P	34	08/05/18	08/05/18	4	MK
28	To take trial with xylitol at concentration of 0.52 mg/mL	C618-23 C618-23P	35	08/05/18	08/05/18	4	MK
29	To take trial with xylitol at concentration of 1.30 mg/mL	C618-24 C618-24P	36	08/05/18	08/05/18	4	MK
20	To take trial batch using enalapril maleate sourced from Inke	C618-25 C618-25P	37	05/06/18	05/06/18	4	MK
31	To take batch for analytical method validation batch formula of B.No. C618-19	C618-26 C618-26P	38	06/06/18	06/06/18	4	MK
32	To take placebo trial without API for Preservation for analytical method validation	C618-27	40	07/06/18	07/06/18	4	MK
33	To manufacture batch for PET Study without antimicrobial preservative (i.e. Methyl paraben and propyl paraben)	C618-28	41	13/06/18	13/06/18	4	MK
34	To manufacture batch for PET Study with antimicrobial preservative at 50% concentration	C618-29	42	13/06/18	13/06/18	4	MK
35	To manufacture batch for PET Study with Antimicrobial preservative at 80% concentration.	C618-30	43	13/06/18	13/06/18	4	MK

Index of Experiments

Product Name: Enalapril maleate oral solution 1mg/mL

Sr. No.	Aim of experiment	Batch No.	Page No.	Initiation Date	Comple. Date	Prep by	Checked by
36	To manufacture batch for PET Study with Antimicrobial preservative at 100% concentration.	C618-31	44	13/06/18	13/06/18	4	MK
37	To manufacture batch for PET Study with Antimicrobial preservative at 20% concentration.	C618-32	45	13/06/18	13/06/18	4	MK
38	To prepare trial batch for analytical method validation purpose	C618-33	46	19/06/18	19/06/18	4	MK
39	To prepare trial batch using formula similar to B.No. C618-33 with slight change in procedure (Preparation of MP and PP solution)	C618-34	47	19/06/18	19/06/18	4	MK
40	To prepare trial batch using formula similar to B.No. C618-35 with minor changes in formula and addition of xylitol	C618-35	48	26/06/18	26/06/18	4	MK
41	To prepare placebo of B.No. C618-35	C618-35P	49	27/06/18	27/06/18	4	MK
42	To prepare batch with all excipients for drug excipient compatibility study.	C618-36 50	50	28/08/18	28/08/18	4	MK
43	To prepare placebo for B.No. C618-36 for compatibility study	C618-36P	51	28/08/18	28/08/18	4	MK
44	To prepare batch with all excipient without citric acid anhydrous for compatibility study	C618-36B	52	24/08/18	24/08/18	4	MK

Index of Experiments

Product Name: Enalapril maleate oral solution 1mg/mL

Sr. No.	Aim of experiment	Batch No.	Page No.	Initiation Date	Comple. Date	Prep by	Checked by
45	To prepare batch with all excipients without sodium Citrate anhydrous for compatibility study	C618-36C	53	24/08/18	24/08/18	J	MK
46	To prepare batch with all excipients without Methyl paraben for compatibility study	C618-36D	54	28/08/18	28/08/18	J	MK
47	To prepare batch with all excipients without propyl paraben for compatibility study	C618-36E	55	28/08/18	28/08/18	J	MK
48	To prepare batch with all excipient except Sucralose for compatibility study	C618-36F	56	29/08/18	29/08/18	J	MK
49	To prepare batch with all excipient except xylitol for compatibility study	C618-36G	57	29/08/18	29/08/18	J	MK
50	To prepare batch with all excipient except mixed berry flavor for compatibility study	C618-36H	58	30/08/18	30/08/18	J	MK
51	To take trial batch using formula of batch no. C618-33	C618-37	60	25/09/18	25/09/18	J	MK
52	To prepare placebo for enalapril maleate oral solution 1mg/mL	C618-37A	61	23/10/18	23/10/18	J	MK
53	To prepare batch with all excipients for drug-excipient compatibility study	C618-38A	62	28/01/19	28/01/19	J	MK

Raw Material Details INDEX OF EXPERIMENTS

Receipt of the Raw material:

Sr. No.	Name of the Raw Material	Batch No.	Received From page no.	Received Date initiation date	Qty received Prep by	Checked by
54	To prepare batch excluding Citric acid anhydrous for drug excipient compatibility study	C618-38B	63	28/01/19	J	MK
55	To prepare batch excluding sodium citrate anhydrous for drug excipient compatibility study	C618-38C	64	29/01/19	J	MK
56	To prepare batch excluding Methyl paraben for drug excipient compatibility study	C618-38D	65	29/01/19	J	MK
57	To prepare batch excluding propyl paraben for drug excipient compatibility study	C618-38E	66	30/01/19	J	MK
58	To prepare batch excluding Sucralose for drug excipient compatibility study	C618-38F	67	30/01/19	J	MK
59	To prepare batch excluding xylitol for drug excipient compatibility study	C618-38G	68	31/01/19	J	MK
60	To prepare batch excluding mixed berry flavor for drug excipient compatibility study	C618-38H	69	31/01/19	J	MK
61	To prepare placebo batch for drug-excipient compatibility study	C618-38P	70	01/02/19	J	MK
62	To prepare placebo for extractable Leachable study purpose	C618-39	71	15/04/19	J	MK

Raw Material Details

solution / answer page no 4

Sr. No.	Name of the Raw Material	Batch No.	Received From	Received Date	Qty received	Checked by
63	To prepare batch for leachable for study for qumy purpose	C618-40	24/01/20	24/01/20	4	Mk
64	To prepare batch with target pH of 2.9	C618-41	73	04/02/20	4	Mk
65	To prepare placebo for batch no. C618-41	C618-41P	74	04/02/20	4	Mk
66	To prepare batch with target pH of 3.0	C618-42	75	04/02/20	4	Mk
67	To prepare placebo for batch no. C618-42	C618-42P	76	04/02/20	4	Mk
68	To prepare batch with target pH of 3.6	C618-43	77	05/02/20	4	Mk
69	To prepare placebo for batch no. C618-43	C618-43P	78	05/02/20	4	Mk
70	To prepare batch with target pH of 3.7	C618-44	79	05/02/20	4	Mk
71	To prepare placebo for batch no. C618-44	C618-44P	80	05/02/20	4	Mk
72	To take repeat trial for batch no. C618-42	C618-45	81	17/02/20	4	Mk
73	perform filter and tube adsorption study using batch no. C618-43 and b No. AAUC08J003	NA	82	18/02/20	4	Mk
74	To take trial for control purpose To plant	C618-046	83	15/02/20	4	Mk

Raw Material Details

Consumption of the Raw material:

[illegible]

Innovator Details

Innovator Characterization:

Sr. No.	Parameters	Observations		
		Strength	Strength	Strength
		1 mg/mL		
1	Brand Name	Epaned [®]		
2	Batch No.	MFEW		
3	Label claim	Each 1 mL contains 1 mg of enalapril maleate eq. to 0.764 mg enalapril.		
4	Mfg. By For	Silvergate pharmaceutical Inc.		
5	Marketed By			
6	Shelf life	04/2019		
	NDC code	NDC 52652-4001-1		
	Physical and chemical Characterization			
	color Appearance	clear colorless	liquid	
	Detection of oxygen in pack of bottle	23.10 %		
	Odor	characteristic odor.		
	pH	3.21		

Critical Discussion Points

IID

Saccharin — oral, solution 10mg/1mL

— oral, granule for suspension 16mg

Sucralose — 40mg/mL, oral solution

Mixed berry flavor — 10mg oral solution

Specific Gravity

C618-01 — 1.003 g/mL

C618-05 — 1.004 g/mL

maximum daily dose — 40mg

Impurity ICI

unknown — 0.2% w/w

known — 0.5% w/w

Done by:



Checked by:



Critical Discussion Points

Patent vs 9,669,008 B1:

Sweetener and preservative incompatibility

Paraben preservatives (especially methyl paraben) reacts with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products.

↑ % Ethanolololol (imp. c) → ↑ pH above 3.5

DKP (impurity-D) slightly ↑ pH → pH at below 4.0

Done by:



Checked by:



Important Dates :

[illegible]

Product: Enalapril maleate oral solution Date: 11/09/2017
1mg/ml

Batch No.: C618-01

Batch Size: 3000ml (20 bottles)

Aim: Trial batch for method development

Procedure:-

- 1) Dissolve saccharin in 2500ml purified water.
- 2) To it add sodium benzoate with stirring, then saccharin.
- 3) Finally add enalapril maleate with continuous stirring.
- 4) Adjust the volume of solution to 3.0L by adding remaining purified water.

pH of solution: 3.35

Done by:

[Signature]
11/09/2017

Checked by:

[Signature]
11/09/2017

Product: Enoxaparin maleate oral solution Date: 11/09/2017
1mg/ml

Batch No.: C618-01

Batch Size: 3000 mL (20 bottles)

[illegible]

potency calculation:

$$\begin{aligned} & \text{Label claim} \times \frac{100}{\text{assay}} \times \frac{100}{(100 - \text{LOD})} \\ &= 1 \times \frac{100}{100.43} \times \frac{100}{(100 - 0.21)} \\ &= 1 \text{ mg/tablet} \end{aligned}$$

Product: Enalapril maleate oral solution Date: 11/10/2017
mg/ml

Batch No.: C618-02

Batch Size: 3000 mL (20 bottles)

[illegible]

potency calculation

$$x = \text{Label claim} \times \frac{100}{\text{Assay}} \times \frac{100}{(100-100)}$$

$$= 1 \times \frac{100}{100.43} \times \frac{100}{(100 - 0.24)}$$

$$= 1 \times 0.996 \times 1.002$$

$\approx 0.99\%$

$$x = 1 \text{ mg/mL}$$

Product: Enalapril maleate oral
solution 1mg/ml

Date: 11/10/2017

Batch No.: C618-02

Batch Size: 3000 ml (20 bottles)

Aim: To prepare batch same as Innovator formula

procedure:

1) 2.5L of purified water is taken into ss container

2) Citric acid, Sodium citrate, Sodium benzoate, Sucralose and berry flavor are dissolved into purified water of step-1 under stirring to get clear solution.

5) Enalapril maleate is added to solution of Step-2 under stirring and stirred to get clear solution.

434

pH of solution before volume makeup = 3.29

4) volume of solution of step-3 is made up to 3L with purified water.

pH of solution after volume make up = 3.32

5

pH of solution initial = 3.32

pH of solution after 16 hrs = 3.35

pH of solution after 4 hrs = 2.33

Done by:

Matpate
11/10/2017

Checked by:

Ms
9/10/2017

RESEARCH ARTICLE

Physicochemical stability of captopril and enalapril extemporaneous formulations for pediatric patients

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No. 19-2100 (MSG)

PTX-78

Abstract

The prevalence of hypertension among children has been increasing. Community and Hospital Pharmacists are often challenged to provide an oral liquid extemporaneous formulation for pediatric patients, because there are no appropriate dosage drugs to the specific needs of the child. The objective of this study is to choose and develop suitable pediatric extemporaneous formulations for captopril and enalapril maleate and to determine their physicochemical stability. A survey was carried out to evaluate the extent of dispensation of these drugs in Hospitals in Spain. Stability studies of formulations have been studied according to ICH normative at 5, 25 and 40 °C. Three samples from each temperature were withdrawn and assessed for stability on days 0, 15, 30, 50 and 90 using a high-performance liquid chromatography (HPLC) mass spectrometer assay. Rheological studies were carried out to ensure the maintenance of the physical characteristics of these non-Newtonian fluids. Captopril and enalapril maleate formulations used the pure drug and were stable during 50 days at 5 °C. We have developed easy antihypertensive oral liquid extemporaneous formulations for pediatric patients with physical and chemical stability higher than those provided by the majority of Hospitals.

Keywords

Compounding, hypertension, rheology

History

Received 19 September 2013

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Published online 26 November 2013

Introduction

Hypertension has now become one of the most prevalent chronic diseases of childhood. The prevalence of pediatric hypertension has increased over the past several decades, bringing with it increased numbers of children with hypertensive effects such as left ventricular hypertrophy as well as greater numbers of hypertensive adults. Although the exact prevalence and incidence of pediatric hypertension are unknown, one study estimated the prevalence to be 4.5% after three separate screenings were conducted on a group of more than 4000 children aged 10–19 years¹. But, despite increasing the number of available anti-hypertensive agents and clinical trials in children, selecting the most appropriate agent and effectively treating high blood pressure remains a challenge.

The first Angiotensin Converting Enzyme (ACE) inhibitor developed, captopril, has been widely studied in children. ACE inhibitors act on the renin–angiotensin system by inhibiting the conversion of angiotensin I to angiotensin II. Compared with other antihypertensive agents, ACE inhibitors now have the largest amount of evidence to support their use in the pediatric population. Beginning with captopril in the 1980s, the data supporting the safety and efficacy of these agents in pediatric patients have grown. Currently, no studies have shown a benefit of one ACE inhibitor over another, even in the adult population. However, one disadvantage of captopril is its mean half-life of

1.5 h (range: 0.98–2.3 h), which is the shortest of all the ACE inhibitors and necessitates frequent dosing – at least twice a day and as often as four times per day – to achieve adequate blood pressure control². Due to that fact, it has been substituted by ACE inhibitor of prolonged action, some of these recently studied in children³. Enalapril has been studied in children^{4–8} and offer once-daily dosing, improving the likelihood of patient compliance compared with agents given more frequently such as captopril. For example, there are good results of dose–response study of the effectiveness and safety of enalapril⁷.

Antihypertensive doses for children are adjusted by body weight, which presents quite an inconvenience when the formulation is displayed only in solid dosage form. For this reason, preparing liquid formulations using tablets is one of the most common practices employed to adjust doses for pediatric patients⁹. Community and hospital pharmacists are often challenged to provide an oral liquid pediatric extemporaneous formulation (PEF). Many times reformulations are demanded from adult dosage forms, because there is no market formulation that allows dosed in such a wide range, or laboratory that produces so many presentations, despite not being legal. The Pediatric Compounding is responsible for providing at any time, regardless of market availability, appropriate dosage drugs to the specific needs of the child. These new dosage forms must be safe and effective by using the pure drug and with the limitations of the excipients that the European Medicines Agency recommended. But, normally any dose or stability control is done in a pharmacy or in a hospital due to the effort which means to keep a stability indicating high-performance liquid chromatography (HPLC) method for every formulation prepared¹⁰. Preparations should allow flexibility in

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dosing and ease of administration, always within limits documented stability from the point of view of chemical and microbiological. It should be avoided undesirable drug, especially those with a narrow therapeutic margin¹¹.

As indicated above, the oral dosage form suitable in this case must be liquid, and the majority solvent is water. Some active ingredients required a certain range of pH in medium to be solubilized in this solvent. In these cases, it is necessary to prepare a suitable buffer solution. Like that, although some active ingredients are completely soluble in water, require a certain pH range to achieve maximum stability in aqueous solution, and in such cases, the pH must be adjusted to the requirements of stability of the preparation. It is advisable that these preparations should not incorporate preservatives since they, even in very small quantities, can cause non-specific reactions or even allergies, and any other kind of sensitizations. For example, those produced by the group “parabens” present in the *p*-hydroxybenzoate (methyl and propyl parabens) and potentially can cause allergic reactions to many other small molecules allergen. Especially sensitive to these reactions are premature infants, newborns and toddlers.

The development of a PEF is not without risk, since any error in the preparation can have serious consequences due to: aqueous solutions are easily contaminable and there is a possibility of dosing errors. For this reason, there are often limited data to support the stability or bioavailability of the final liquid dosage form, where potential interactions have yet to be established between the vehicle, preservative, buffering agent, flavoring agent, suspending agent, storage container and the modified commercial product.

In sum, there is not always a specialty child prescribe. In Spain there is a shortage of pediatric specialties marketed¹¹. There are many factors that determine the lack of cost-effectiveness of this market of commercial pediatric oral liquid forms. Clinical studies adequate for pediatric labeling of drugs are often more costly, pose patient recruitment challenges, encompass unique ethical and practical issues and involve greater potential liability than comparable studies carried out in adult populations^{12–14}. Also, the complexity of the development of an oral liquid form due to the unstable drugs in aqueous vehicles and all the adverse side effects of the conventional excipients¹⁵.

The Pediatric Compounding is a real need that cannot be changed by other medicines. For this reason, it is fundamental a close cooperation between Colleges of Pharmacists, raw material distributors, formulaic associations and University to enhance Compounding. And also, it is necessary that all these formulas developed should be characterized by their quality and traceability. For this objective, it is essential to develop regulations governing such elaboration, and that it meets the really needs of pediatric patients.

Thus it was created a working group formed by the Instituto Tecnológico del Medicamento Individualizado (ITMI from Spain), Acofarma (Barcelona, Spain), Fagrón (Barcelona, Spain), University Hospital Virgen del Rocío of Seville (Spain), Community Pharmacists and the Department of Pharmacy and Pharmaceutical Technology, University of Seville (Spain).

The objective of this study is to choose and develop suitable pediatric extemporaneous formulations for the most used antihypertensive drugs: captopril and enalapril maleate; and to determine their physicochemical stability. For this aim, we have worked with the most important Hospitals of Spain and the ITMI with the objective of unifying criteria in pediatric formulations. And then, these PEF could be reproduced by a simple and feasible Standard Operating Procedure for its use by Pharmacist both in Community and Hospital Pharmacy.

Materials and methods

Materials

Captopril and enalapril maleate were used as antihypertensive drugs (Acofarma, Barcelona, Spain). Both drugs are white to off-white, crystalline powders, but captopril is freely soluble, while enalapril maleate is sparingly soluble in water. Simple syrup (Guinama, Alboraya, Spain), edetate disodium (Fagron, Barcelona, Spain), citric acid (Acofarma, Barcelona, Spain), chlorhydric acid, sodium hydroxide (Panreac, Barcelona, Spain) and purified water were used for the preparation of formulations. All chemicals and reagents used in this study were analytical grade materials. HPLC-grade methanol and formic acid were purchased from Merck (Darmstadt, Germany). Deionized water ($>18\text{ M}\Omega\text{ cm}^{-1}$ resistivity) was obtained from a Milli-Q water purification system (Millipore, Bedford, MA).

Survey of Hospitals

A survey was carried out to evaluate the extent of dispensation of captopril and enalapril maleate PEF in 20 Hospitals in Spain (Tables 1 and 2). The questionnaire was designed to determine the source (i.e. whether extemporaneously prepared or procured from an external special manufacturer), and the identity of the external source if one was used. In addition, the survey asked for any data available on the composition and properties of the extemporaneously prepared oral liquid formulas in the Hospitals, including vehicle, other excipients, stability and expiration date. It has been included also in the tables the formulations described by International Journal of Pharmaceutical Compounding and Ph. D Atienza Manual¹⁶.

Pediatric extemporaneous formulations

We have developed two pediatric extemporaneous formulations (PEF) (Table 3) that a Pharmacist could easily prepare with available and low cost materials, taking into account all the information provided by Hospitals, reported in Tables 1 and 2. Both PEF have 1 mg/ml drug concentration in order to simplify the dosage from the medical prescription.

For captopril PEF: edetate disodium (0.01% w/v), used as preservative, was dissolved in the purified water and then captopril (0.1% w/v) was added under stirring until completely dissolution.

For enalapril maleate PEF: buffer solution was prepared with citric acid (0.592 w/v), HCl 0.1 M (0.409 v/v), NaOH 1 M (0.057 v/v) and purified water (0.284 v/v). Then, enalapril maleate (0.1% w/v) was added to dissolve and the final volume was adjusted with simple syrup, as suspending and sweetener agent, under stirring.

About 500 ml of each formula have been prepared and distributed in opaque glass and light protected bottles (30 ml) to the stability study, keeping one aliquot for the time zero and quality control.

pH determination

The pH was tested in triplicated by a pHmeter Crison GLP 21 (Barcelona, Spain) immediately after the PEF preparation and on each sampling day.

Rheological properties

Multi-step flow curve measurements were run using a controlled stress rheometer (AR-2000, TA Instruments, New Castle, DE), using a geometry of 60 mm diameter with smooth surface. All measurements were made at $25 \pm 0.1^\circ\text{C}$ on Peltier plate. The experimental protocol consisted of applying every shear stress either until an approximation to the steady-state of 0.001 was

Table 1. Captopril PEF made by different Hospitals, or described by Int. Pharm. Compounding and Ph. D Atienza Manual.

Hospital	Captopril dose	Composition	Stability
Gregorio Marañón	1 mg/ml solution	Captopril PH EUR Ascorbic acid 0.5 % Distilled water	28 days at 25 °C 2 months at 5 °C
Cruces	1 mg/ml solution	Capoten® tablets Purified water	15 days at 5 °C
Juan Ramón Jiménez	1 mg/ml solution	Captopril Ascorbic acid 0.5% Conservans water 5% Simple syrup	15–56 days at 5 °C
Clarion	1 mg/ml solution	Captopril Ascorbic acid 0.5% Sodium Sacarine 0.4% Raspberry concentrated solution Purified water	28 days at 5 °C
Principado de Asturias	1 mg/ml solution	Captopril Ascorbic acid 0.5% Versylene water	56 days at 5 °C
Alicante	2 mg/ml solution	Captopril Ora-sweet® 50% Ora-plus® 50%	7 days at 25 °C 3 months at 5 °C
Torrecedenas, Jaén, Miguel Servet, Málaga, Valdecilla	1 mg/ml solution	Captopril Sterile water for irrigation 30% Sodium ascorbate 0.5% Simple syrup	43 days at 5 °C
La Paz	1 mg/ml solution	Captopril Purified water	15 days at 5 °C
Virgen de las Nieves	1 mg/ml solution	Captopril Sodium Bi-Edetate 0.1% Sterile water	1 year at 5 °C 1 month once open
San Joan de Deu	1 mg/ml solution	Captopril Disodium edetate 0.1% Bidistilled water	90 days at 5 °C 30 days once open
Gran Canaria	1 mg/ml solution	Captopril Ascorbic acid 0.1% Bidistillated water	56 days at 5 °C
Vall d'Hebrón	2 mg/ml solution	Captopril 210 mg Acid citric monohydrate 250 mg Sodium citric dihydrate 300 mg Sodium benzoate 100 mg Ascorbic acid 50 mg Sorbitol solution 70% 22 mg Strawberry essence 8159 Sterile distilled water 76 ml	30 days at 5 °C 7 days at 25 °C
Int. J. Pharm. Compounding	0.75 mg/m solution	Captopril tablets Ora-sweet® 50% Ora-plus® 50%	7 days at 25 °C 14 days at 5 °C
Ph D. Atienza Manual	1 mg/ml solution	Captopril Sterile water for irrigation 30% Sodium ascorbate 0.5% Simple syrup	43 days at 5 °C

reached or until a maximum time of 300 s per point. First of all, the linear viscoelastic region for the different systems was determined by stress sweeps at 1 Hz. With these results it is selected the stress amplitude to determine the mechanical spectra in a frequency range from 0.01 to 100 rad/s. On the other hand, for rotational shear assay, it has been determined flow and viscosity curves.

According to the shear stress/shear rate behavior, a rheological classification of materials can be made. Among them, Newtonian and non-Newtonian materials are the most important in the

pharmaceutical field. A Newtonian fluid is characterized by keeping the Law of Newton¹⁷, i.e. that linear ratio exists between the shear stress (τ) and shear rate ($\dot{\gamma}$). In this case, viscosity (η) is a constant and does not depend on the shear stress applied or shear rate [Equation (1)]:

$$\tau = \eta \cdot \dot{\gamma} \quad (1)$$

Non-Newtonian fluids are those in which there is not a linear ratio between the shear stress and the shear rate, i.e. not follow the law

Table 2. Enalapril PEF made by different Hospitals, or described by Int. Pharm. Compounding and Ph. D Atienza Manual.

Hospital	Enalapril dose	Composition	Stability
Torrecedenas, Cruces, Jaén, Miguel Servet, Juan R Jiménez	1 mg/ml solution	Enalapril maleate Buffer citrate pH 3-3.5 Simple syrup	200 mg 150 ml 50 ml 1 month at 5 °C
Gregorio Marañón, Puerta del Mar-Cádiz, Gran Canaria, Vallecilla - Santander	1 mg/ml suspension	Enalapril maleate Ora Sweet®:Ora Plus® 1:1 q.s. to	100 mg 100 ml 91 days at 5 °C
La Paz	1 mg/ml suspension	Enalapril Ora-Plus:Ora-Sweet 1:1	40 mg 40 ml 56 days at 5 °C
Sick Kids Pharmacy, Virgen de las Nieves, Niño Jesús, Principado de Asturias	1 mg/ml suspension	Enalapril in tablets Oraplus®: Orasweet®	60 days at 5 °C
Vall de Hebron	1 mg/ml suspension	Enalapril (Renitec® 20 mg) Ora-sweet® Ora-plus®	6 tablets 60 ml 60 ml 56 days at 25 °C 91 days at 5 °C
Vallecilla – Santander	1 mg/ml suspension	Enalapril maleate (5 tablets of 20 mg) Citric acid monohydrate Sodium citrate dehydrate Parabens solution Water for injection Q.S to	100 mg 0.35 g 1 g 1 ml 100 ml 1 month at 5 °C
Int. J. Pharm. Compounding	1 mg/ml suspension	Enalapril in tablets Oraplus®: Orasweet®	60 days at 5 °C
Ph. D Atienza Manual	1 mg/ml solution	Enalapril maleate Buffer citrate pH 3-3.5 Simple syrup	200 mg 150 ml 50 ml 1 month at 5 °C

Table 3. Captopril and enalapril maleate PEF composition.

Captopril 1 mg/ml		Enalapril 1 mg/ml	
Captopril	100 mg	Enalapril maleate	100 mg
Edetate disodium	10 mg	Citric acid	592 mg
Purified water q.s to	100 ml	HCl 0.1 M	40.9 ml
		NaOH 1 M	5.7 ml
		Purified water	28.4 ml
		Simple syrup q.s to	100 ml

of Newton. In this case, instead of viscosity there is another parameter called apparent viscosity (η_{ap}) which is a function of shear rate. This behavior is found in many complex fluids, emulsions, suspensions and polymer systems used in pharmaceutical industry. Based on the flow and viscosity curves, the non-Newtonian fluids can be classified as follows: pseudoplastic, plastic, dilatant and structural¹⁸.

Different theoretical models can be used to treat the rheological results. Taking into account that these PEF are very fluids, the best fit is the Ostwald-De Waele or Power law model [Equation (2)]:

$$\tau = k\dot{\gamma}^n \quad (2)$$

In this model, the viscosity is replaced by a consistency index, k , which relates the shear stress τ and the shear rate $\dot{\gamma}$. A new parameter called flow index or index deviation from Newtonian behavior, n , distinguish three basic types of materials: Newtonian ($n=1$), plastic or pseudoplastic ($n<1$) and dilatants ($n>1$)¹⁹.

Analytical method

Enalapril maleate and captopril were identified using a PelkinElmer Series 200 HPLC system (Wellesley, MA) coupled to an Applied Biosystems QTRAP LC/MS/MS system (Foster City, CA) consisting of an hybrid triple quadrupole linear ion trap (QqQLIT) mass spectrometer equipped with an electrospray ion

source. HPLC analyses were performed on a 150×2.1 mm (3.5 μ m) Zorbax Sb-Aq column at room temperature (25 °C). Chromatographic separation was performed using a binary gradient consisting of (A) water, and (B) methanol, both components contained 0.1% formic acid (v/v). Injection volume was 20 μ l. The elution profile was: 10 % B (2 min), linear gradient to 100 % B (8 min), 100 % B (2 min) and finally 10% B (3 min). The flow rate was 0.25 ml/min and the run time was 15 min.

Multiple Reaction Monitoring (MRM) experiment was applied where the parent ions and fragments ions were monitored at Q1 and Q3, respectively. The transitions for captopril are: 218.2/70.0, 218.2/171.8 and 218.2/115.9, and for enalapril maleate are: 377.3/234.0 and 377.0/303.1. The majority transitions 218.2/70.0 and 377.3/234.0 were chosen for quantitation of captopril and enalapril maleate, respectively.

For HPLC-ESI-MS/MS analyses, the mass spectrometer was set to the following optimized tune parameters: curtain gas 35 psi, ion spray voltage 5500 V, source temperature 350 °C, source gas 60 psi.

In order to validate the analytical method, six standard solutions of each drug were prepared at concentrations of 50-1000 ng/ml. Every sample was analyzed three times. The variance analysis (ANOVA) of the linear regression confirmed the linearity of the method through rejection of the null hypothesis of linearity deviation for a significance level of 0.05 ($\alpha=0.05$). The coefficients of variation of the method were 2.9 and 3.6% for captopril and enalapril, respectively. The equations of the regression line were: $2.23e+003 x + -2.14e+004$ ($r=0.9996$; $n=18$) for captopril and $87.4 x + -6.88e+003$ ($r=0.9943$; $n=18$) for enalapril maleate.

Stability studies

Three month stability testing of the PEF was conducted in opaque glass and light protected bottles as described by the ICH Q1A (R2)²⁰. Bottles of 30 ml were stored at climatic cameras (CCI Lab, Barcelona, Spain). Storage conditions were 5 ± 3 °C (further referred to as only as 5 °C) and for accelerated stability

$25 \pm 2^\circ\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ (RH: relative humidity) (referred to as 25°C) and $40 \pm 2^\circ\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$ (referred to as 40°C). Three samples of each temperature were withdrawn and tested at 15, 30, 50 and 90 days (if the drug content were higher than 95%). Analysis included pH, rheological properties and drug content. Expiration data were established when formulations show the 95% of declared drug.

Results

Survey of Hospitals

The review of the different antihypertensive formulations developed by Hospitals in Spain reveals a wide disparity in both composition and stability of the PEF, although all they agree on keeping at 5°C .

Focusing on captopril preparations, we can see that all Hospitals except one, use the pure drug, and the majority stabilize the formulation with ascorbic acid or its salts. However, captopril solution with the maximum stability (90 days) is those with edetate disodium. The reason of that higher stability could be due to its chelating property, which slows oxidation reactions catalyzed by metals. The two Hospitals that only add water to the drug are precisely those with formulas more unstable. The instability of captopril in solution is due to the degradation by oxidation of the sulfhydryl group. Many authors have developed different extemporaneous solution to avoid the problem of stability²¹. Other researchers have studied the stability of this drug in solutions and they have related the stability with the water characteristics used as a vehicle²². Also, it has been studied the influence of chelating agents such as edetate disodium to remove the metal ions present in the solution, showing that solutions are more stable with this excipient^{16,21}. Moreover, other authors have tested the stability of captopril in solutions prepared with ascorbic acid and sodium ascorbate as antioxidant in order to prevent oxidation of captopril, proving that formulas without antioxidants and pH modifiers are the most stable²¹. Also, stability of captopril in syrup and invert sugar solution has been analyzed²². There are also works in which it has been studied the influence of temperature on the conservation of captopril solutions²¹.

With respect to formulas of enalapril maleate, half of the Hospitals surveyed used market tablets and they only add a mixture of Ora-Plus[®]:Ora-Sweet[®] 1:1, thereby obtaining a suspension. As occurred with captopril, the maximum time they are stable is around 90 days. The chemical and physical stability of enalapril maleate has been studied by several workers. It is reported to be fairly stable when stored in closed containers, but shows instability in open containers and on exposure to high temperature and humidity, leading to the formation of two major degradation products: enalaprilat (by hydrolysis) and a diketopiperazine degradation product (by intramolecular cyclization)^{23–26}. These products are reported to be formed in solutions of pH above and below 3, respectively, and even in tablets^{23,27}. The degradation of enalapril maleate is pH dependent. In solutions above pH 5, enalapril maleate forms the poorly absorbable enalaprilat²⁸. Enalapril maleate is also shown to be photolabile in solution, yielding diketopiperazine derivative as the main degradation product. Several vehicles have been used by Pharmacists for extemporaneous solutions, such as water, citrate buffers and commercially available vehicles (e.g. Ora-Sweet[®] and simple syrup). However, only limited chemical stability, microbial sterility, appearance and storage conditions are known for many of these medications after they are prepared extemporaneously. Despite several publications that address this in part^{28–33}, only limited information on a handful of active ingredients is available.

Currently, the marketed form of enalapril, Vasotec[®] (Merck&Co., Inc.), contains labeling directions to prepare 200ml of a 1.0mg/ml suspension. The suspension contains Bicitra[®] and OraSweet[®], is refrigerated and is stable for up to 30 days. Other solutions/suspensions of enalapril have been studied with varying success^{13,28,32}.

With all this information and taking into account the composition of the PEF mentioned above with better stability, we have made formulations according to the “PEF method” section (Table 3). In our PEF, we have used the pure drug to eliminate the need for manipulating commercial tablets. Starting with captopril, we have chosen the PEF with the maximum stability, provided by Hospital San Joan de Deu, with edetate disodium, but in contrast with this Hospital, we have added only 0.01% instead of 0.1%, to minimize adverse effects. Respect to enalapril maleate, we have formulated with citric acid to guarantees the drug stability, and commercial simple syrup to standardized the PEF.

Oral liquid PEF were stored and evaluated at three temperatures and RH during 3 months. The two PEF were transparent solutions and there has been no change in color during the study at different temperatures. However, after 50 days, captopril PEF stored at 25 and 40°C show microbiological contamination, so these PEF were discarded. For enalapril maleate PEF the same happens at 25 and 40°C , but in this case the microbiological contamination appears at 30 days.

pH determination

The pH of the formulations was measured at time zero and at each sampling time. Figure 1 shows the pH values at different times and temperatures of captopril and enalapril maleate PEF. No variations of pH have been observed with temperature or time of storage within 50 days of study. Captopril PEF have pH values in the interval of 2.85–3.04, while enalapril maleate PEF were slightly acidic values, between 2.55–2.78. Therefore, the pH maintenance of these formulations for these acidic drugs guarantees the drug stability.

Rheological properties

Regarding rheological properties, in oscillatory study stress and frequency sweeps indicate that PEF are non viscoelastic fluids, as there is no elastic component (G') but only the viscous moduli (G'') (data not shown). With respect to rotational study, the shear stress and shear rate parameters (Figures 2 and 3) show the influence of time or temperature on the flow curves of captopril and enalapril PEF, respectively. The two PEF have a behavior of non-Newtonian fluids, as viscosity does not remain constant as the shear rate changes. As it can be seen, there is a little variation of values with the time and the temperature, more marked in the case of enalapril PEF. The curves were fitted to the Power law and consistency (k) and flow (n) index are shown for each formulation in the figures. As observed, the consistency of the PEF is very small, in the order of 10^{-4} – 10^{-5} Pa s, as liquids like water. Also, k values decrease with the increase of time or temperature. Although captopril PEF have n values of 0.98 at time 0, indicating a like pseudoplastic flow, with the storage time this behavior is modified to a dilatant one (n between 1.4–1.5). The dilatant behavior is characterized by the increase of viscosity with the shear rate, but in captopril PEF this phenomenon is not significant due to the small viscosity variations observed.

For enalapril PEF, the rheological behavior observed is similar to captopril PEF. Only, the main difference is a higher pseudoplastic flow at time 0 ($n = 0.70$).

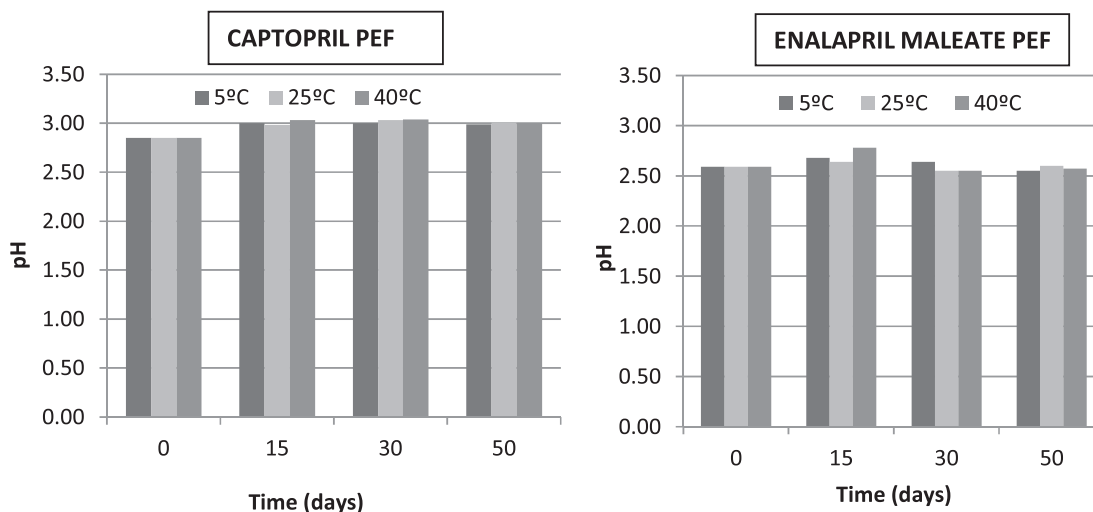


Figure 1. pH values of captopril and enalapril PEF at different temperatures and times studied.

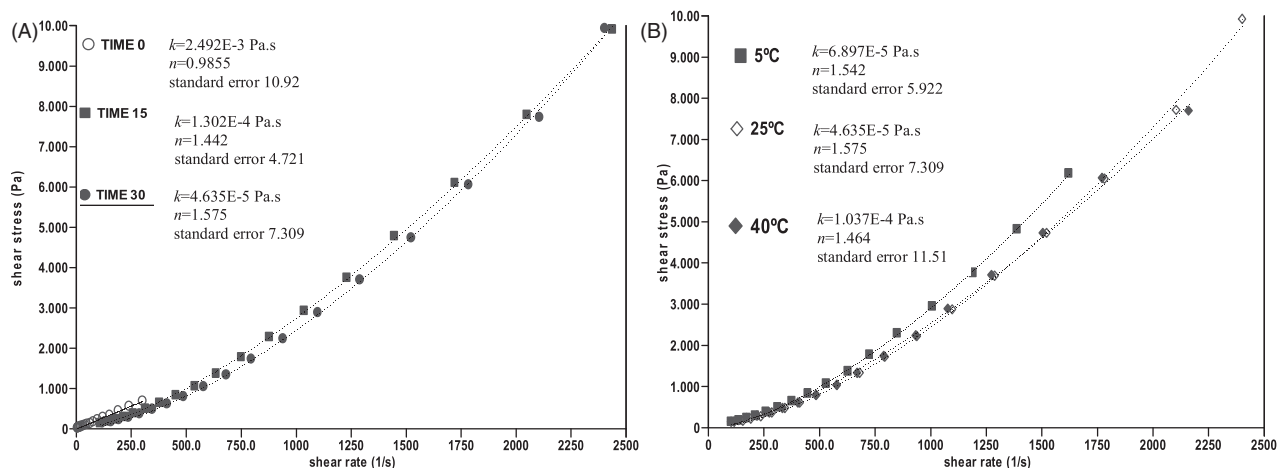


Figure 2. Shear stress versus shear rate of captopril PEF at times studied at 25°C (A) and temperatures indicated at time 30 (B).

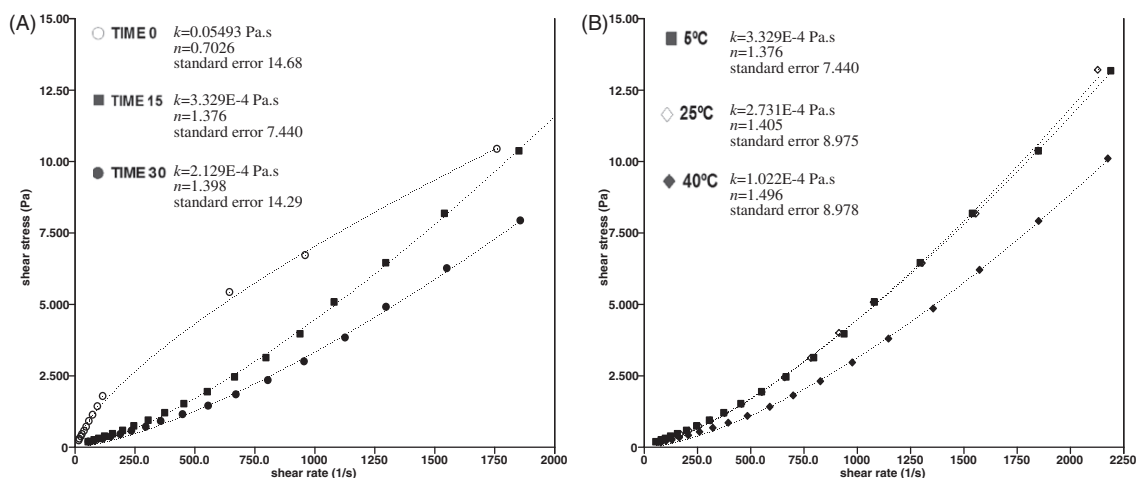


Figure 3. Shear stress versus shear rate of enalapril PEF at times studied at 5°C (A) and temperatures indicated at time 30 (B).

Stability studies

Regard to the stability studies, analytical method allowed to quantify the drugs at different times studied. Figure 4 shows captopril and enalapril maleate HPLC-mass results. Enalapril

appears at retention time of 8.7 min (A) and captopril at 8.6 (B). Respect to drug content, Figure 5 shows that PEF are more stable at 5°C than at the upper temperatures. For captopril PEF, until 30 days the drug content values were above the 95% for all the temperatures [100 (0.33), 98 (0.45) and 97% (0.61) for 5, 25 and

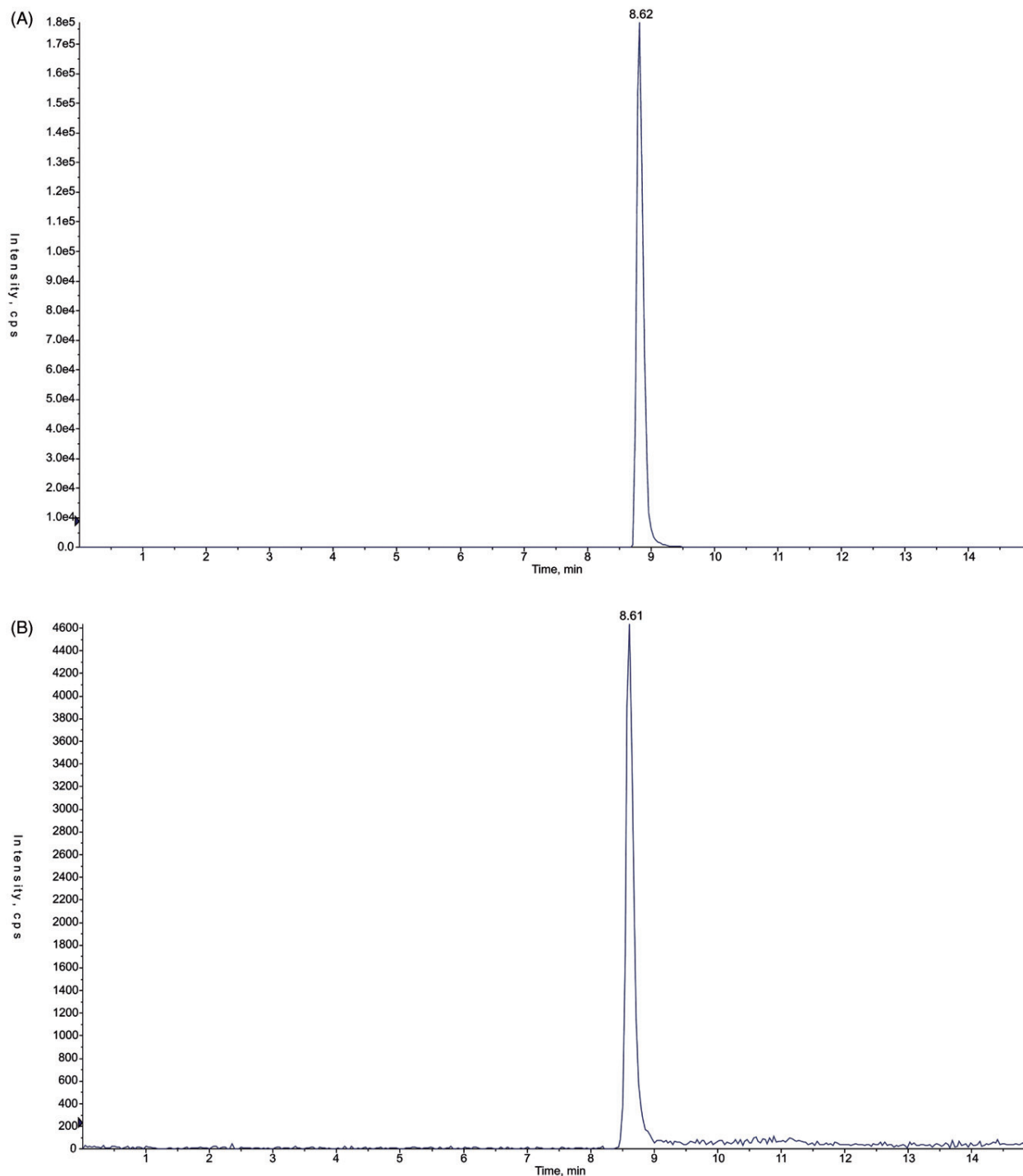


Figure 4. Mass spectrometer of enalapril (A) and captopril (B).

40 °C, respectively]. But, at 50 days, the values decrease until 97 (0.51), 86 (0.42) and 82% (0.66), respectively. For enalapril PEF, the drug content was above the 95% until 50 days of study for 5 and 25 °C, decreasing below this value only in the case of 40 °C. After 3 months of study, at the three temperatures studied drug content of PEF decreased by 40%.

Discussion

Criteria homogenization is considered essential in the development of pediatric extemporaneous formulations (PEF) both Community Pharmacy and Hospital Pharmacy level. Taking into account the extemporaneous formulas provided by Hospitals

of Spain, we have developed PEF for the most used antihypertensives: captopril and enalapril maleate. PEF use the pure drug, unlike many Hospitals that use commercial tablets, to eliminate the need for manipulation, and were easy and reproducible. Physical and chemical stability of extemporaneous formulations has been studied according to ICH normative. PEF were transparent solutions with acidic pH values to guarantee the drug stability. No significant alterations were detected throughout the 50 day study at 5 °C. Rheological results show a non-Newtonian behavior (Power law model) for the PEF with a pseudoplastic and dilatant flow. The consistency index values of PEF were very small and decrease with the time or upper temperatures. On the other hand, according to drug content

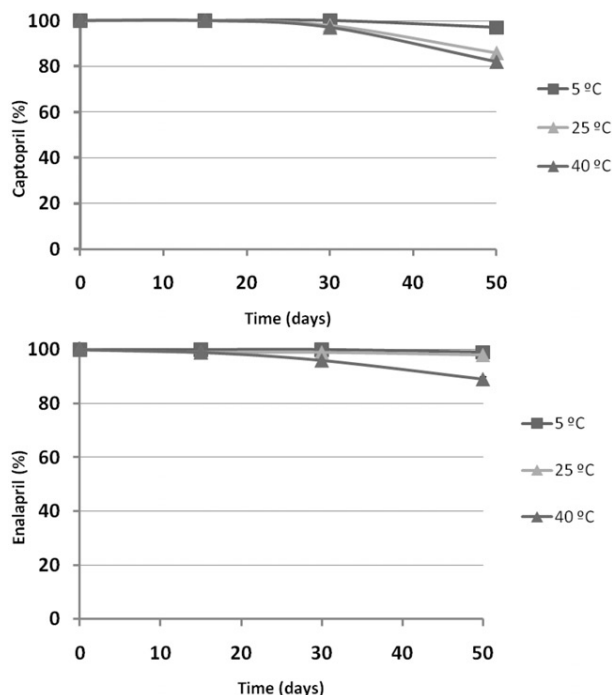


Figure 5. Captopril and enalapril maleate concentrations at the times and temperatures indicated.

results, PEF were more stable at 5 °C than at 25 or 40 °C. Like this, we propose an expiration date of 50 days keeping at 5 °C, or 30 days at room temperature to captopril and enalapril maleate PEF. In summary, we have achieved antihypertensive extemporaneous formulations for pediatric patients with physical and chemical stability higher than those provided by the majority of Hospitals and suitable to be prepared for any Pharmacists.

Declaration of interest

The authors report no declarations of interest.

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1 UNITED STATES DISTRICT COURT

2 DISTRICT OF DELAWARE

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4 x

5 AZURITY PHARMACEUTICALS, :

6 INC., :

7 Plaintiff, : C.A. No. 19 2100

8 v. : (LPS) (CJB)

9 ALKEM LABORATORIES LTD., :

10 Defendant. :

11 x

12
13 Virtual Videotaped Rule 30(b)(6) Deposition of

14 Azurity Pharmaceuticals

15 DR. GEROLD MOSHER

16 Tuesday, February 8, 2022

17 8:59 a.m. CST

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20
21 Job No.: 429464

22 Pages: 1 178

23 Reported by: THERESA A. VORKAPIC,

24 CSR, RMR, CRR, RPR

Transcript of Gerold Mosher
Conducted on February 8, 2022

10

1	[REDACTED]	09:04:21
2	[REDACTED]	09:04:23
3	[REDACTED]	09:04:29
4	Can you tell me when the first time you	09:04:31
5	worked on a liquid oral formulation, drug	09:04:33
6	formulation?	09:04:40
7	[REDACTED]	09:04:40
8	[REDACTED]	09:04:41
9	BY THE WITNESS:	09:04:45
10	A I believe I had one development project at	09:04:45
11	Eli Lilly and Company around 1987.	09:04:48
12	[REDACTED]	09:04:55
13	[REDACTED]	09:04:55
14	[REDACTED]	09:04:58
15	[REDACTED]	09:04:58
16	[REDACTED]	09:05:01
17	[REDACTED]	09:05:01
18	[REDACTED]	09:05:05
19	[REDACTED]	09:05:08
20	[REDACTED]	09:05:09
21	[REDACTED]	09:05:10
22	[REDACTED]	09:05:13
23	[REDACTED]	09:05:16
24	[REDACTED]	09:05:18
25	[REDACTED]	09:05:26

Transcript of Gerold Mosher
Conducted on February 8, 2022

12

1	[REDACTED]	09:06:30
2	[REDACTED]	09:06:35
3	[REDACTED]	09:06:35
4	[REDACTED]	09:06:37
5	[REDACTED]	09:06:39
6	[REDACTED]	09:06:43
7	Q Well, we can go ahead and do that. I	09:06:48
8	don't know that I have the most current version,	09:06:51
9	but if we could pull up Tab 25, and we'll mark	09:06:53
10	that as Exhibit 1.	09:06:55
11	[REDACTED]	09:06:57
12	[REDACTED]	
13	[REDACTED]	09:07:17
14	[REDACTED]	09:07:17
15	[REDACTED]	09:07:19
16	[REDACTED]	09:07:23
17	[REDACTED]	09:07:24
18	[REDACTED]	09:07:25
19	[REDACTED]	09:07:27
20	[REDACTED]	09:07:29
21	[REDACTED]	09:07:36
22	[REDACTED]	09:07:38
23	[REDACTED]	09:07:40
24	[REDACTED]	09:07:41
25	[REDACTED]	09:07:44

Transcript of Gerold Mosher
Conducted on February 8, 2022

13

1	[REDACTED]	09:07:44
2	[REDACTED]	09:07:45
3	[REDACTED]	09:07:47
4	[REDACTED]	09:07:48
5	[REDACTED]	09:07:58
6	[REDACTED]	09:08:01
7	[REDACTED]	09:08:02
8	[REDACTED]	09:08:04
9	[REDACTED]	09:08:06
10	[REDACTED]	09:08:21
11	[REDACTED]	09:08:23
12	Q Dr. Mosher, we've put up and made	09:08:27
13	available to you what's been marked now as	09:08:28
14	Exhibit 1 to your deposition which appears to me	09:08:31
15	to be a copy of your CV. If you could please	09:08:33
16	review that and let me know when you've had a	09:08:36
17	chance to review it, and we can go from there.	09:08:39
18	I'll start with my last question.	09:08:42
19	A Yes. [REDACTED]	09:09:01
20	[REDACTED]	09:09:03
21	[REDACTED]	09:09:37
22	[REDACTED]	09:09:48
23	[REDACTED]	09:10:01
24	[REDACTED]	09:10:03
25	[REDACTED]	09:10:05

Transcript of Gerold Mosher
Conducted on February 8, 2022

23

1	[REDACTED]	09:22:39
2	[REDACTED]	09:22:44
3	[REDACTED]	09:22:45
4	[REDACTED]	09:22:47
5	[REDACTED]	09:22:55
6	Q Following college, going back over the	09:22:57
7	formulations that you identified that you've	09:23:01
8	worked with in the past, let's start with the Eli	09:23:03
9	Lilly formulation in 1987, do you recall which	09:23:07
10	buffers you worked with for that product?	09:23:11
11	[REDACTED]	09:23:14
12	[REDACTED]	09:23:17
13	[REDACTED]	09:23:19
14	A Due to the nature of that compound, I	09:23:19
15	would have to speculate, but it was likely	09:23:21
16	acetate, fumarate, maleate, probably citrate as	09:23:28
17	well.	09:23:33
18	BY MR. BARRY:	09:23:47
19	Q Thank you.	09:23:47
20	In responding, you said you would have to	09:23:48
21	speculate based on the nature of the product. Can	09:23:49
22	you explain why the nature of the product leads	09:23:53
23	you to need to speculate about which buffers you	09:23:55
24	might have used?	09:23:58
25	[REDACTED]	09:23:59

Transcript of Gerold Mosher
Conducted on February 8, 2022

24

1	[REDACTED]	09:24:00
2	[REDACTED]	09:24:06
3	A The choice of a buffer is oftentimes	09:24:06
4	dictated by the pH of the solution that you wish	09:24:08
5	to achieve and the pKa of the other components in	09:24:12
6	that formulation as well as the pKa of the buffer.	09:24:16
7	[REDACTED]	09:24:26
8	[REDACTED]	09:24:26
9	[REDACTED]	09:24:29
10	[REDACTED]	09:24:30
11	[REDACTED]	09:24:32
12	[REDACTED]	09:24:33
13	[REDACTED]	09:24:33
14	[REDACTED]	09:24:35
15	[REDACTED]	09:24:39
16	[REDACTED]	09:24:47
17	[REDACTED]	09:24:51
18	[REDACTED]	09:24:54
19	[REDACTED]	09:25:00
20	So when you're developing a formulation	09:25:03
21	and you're thinking it may need a buffer, do you	09:25:11
22	first set a target pH and analyze the pKa of the	09:25:16
23	compound before deciding which buffer to use?	09:25:23
24	[REDACTED]	09:25:26
25	[REDACTED]	09:25:27

Transcript of Gerold Mosher
Conducted on February 8, 2022

25

1	[REDACTED]	09:25:31
2	[REDACTED]	09:25:36
3	A My approach is typically to understand the	09:25:37
4	pH range that is desired for a particular	09:25:41
5	formulation, looking at the active ingredient and	09:25:44
6	understanding the pKa of that active ingredient.	09:25:54
7	One then looks at that pKa and would make rational	09:26:02
8	decisions about what might be the appropriate	09:26:06
9	buffer species.	09:26:09
10	BY MR. BARRY:	09:26:10
11	Q Thank you.	09:26:15
12	And if I understand your answer correctly,	09:26:16
13	assessing a compound's pKa would be part of the	09:26:24
14	preliminary steps that you would take in	09:26:28
15	formulating any compound; is that fair?	09:26:32
16	[REDACTED]	09:26:34
17	[REDACTED]	09:26:35
18	[REDACTED]	09:26:42
19	A That is correct.	09:26:43
20	BY MR. BARRY:	09:26:43
21	Q Let's stay on that. I'd like to know more	09:26:44
22	about your process for formulating a drug and	09:26:47
23	obviously you could lecture on it for days, I'm	09:26:53
24	sure, but I'm just curious generally.	09:27:00
25	There is a problem to be solved and you	09:27:05

Transcript of Gerold Mosher
Conducted on February 8, 2022

26

1		09:27:08
2		09:27:13
3		09:27:16
4		09:27:18
5		09:27:19
6		09:27:29
7	A The question is almost too broad to	09:27:30
8	respond to. Could you give me more specifics?	09:27:32
9		
10		09:27:35
11		09:27:37
12		09:27:40
13		09:27:42
14		09:27:47
15		09:27:48
16		09:28:00
17	A I guess typically when I would develop	09:28:00
18	formulations, I would have a target product	09:28:02
19	profile that had been developed by other people to	09:28:05
20	tell me what their desired formulation is and the	09:28:13
21	desired characteristics, and I would formulate	09:28:16
22	towards that profile.	09:28:19
23		09:28:24
24		09:28:28
25		09:28:34

Transcript of Gerold Mosher
Conducted on February 8, 2022

27

1	[REDACTED]	09:28:36
2	[REDACTED]	09:28:37
3	[REDACTED]	09:28:37
4	[REDACTED]	09:28:39
5	[REDACTED]	09:28:41
6	[REDACTED]	09:28:41
7	You said that typically and I realize	09:28:43
8	that doesn't mean in every instance, but typically	09:28:46
9	that you would get you would receive input with	09:28:48
10	a desired formulation and then you would work with	09:28:52
11	to try to create.	09:28:58
12	Did I understand that correctly?	09:29:00
13	[REDACTED]	09:29:02
14	[REDACTED]	09:29:04
15	[REDACTED]	09:29:04
16	A Yes.	09:29:05
17	[REDACTED]	09:29:05
18	[REDACTED]	09:29:06
19	[REDACTED]	09:29:09
20	Q So with respect to Epaned, the reference	09:29:13
21	listed drug product that we're talking about, the	09:29:19
22	solution, not the Epaned powder or oral solution	09:29:23
23	but Epaned solution, in formulating that, did you	09:29:29
24	follow that same process or was the process	09:29:33
25	different?	09:29:36

Transcript of Gerold Mosher
Conducted on February 8, 2022

28

1	[REDACTED]	09:29:36
2	[REDACTED]	09:29:44
3	A It was similar in that I was requested to	09:29:45
4	try to prepare an oral liquid formulation of	09:29:50
5	enalapril.	09:29:54
6	[REDACTED]	09:30:05
7	[REDACTED]	09:30:06
8	[REDACTED]	09:30:07
9	[REDACTED]	09:30:08
10	[REDACTED]	09:30:08
11	[REDACTED]	09:30:09
12	[REDACTED]	09:30:11
13	[REDACTED]	09:30:11
14	Q Sorry. Who made that request of you?	09:30:11
15	[REDACTED]	09:30:19
16	[REDACTED]	09:30:21
17	A My supervisor, Michael Beckloff.	09:30:22
18	[REDACTED]	09:30:28
19	[REDACTED]	09:30:28
20	[REDACTED]	09:30:30
21	[REDACTED]	09:30:37
22	[REDACTED]	09:30:37
23	[REDACTED]	09:30:37
24	[REDACTED]	09:30:39
25	[REDACTED]	09:30:40

Transcript of Gerold Mosher
Conducted on February 8, 2022

29

1	[REDACTED]	09:30:41
2	[REDACTED]	09:30:43
3	[REDACTED]	09:30:50
4	[REDACTED]	09:30:51
5	[REDACTED]	09:30:52
6	[REDACTED]	09:30:54
7	[REDACTED]	09:30:55
8	[REDACTED]	09:31:02
9	[REDACTED]	09:31:06
10	[REDACTED]	09:31:07
11	[REDACTED]	09:31:07
12	[REDACTED]	09:31:10
13	Q Was Mr. Beckloff your supervisor when you	09:31:11
14	joined?	09:31:13
15	[REDACTED]	09:31:18
16	[REDACTED]	09:31:20
17	[REDACTED]	09:31:21
18	A Yes.	09:31:21
19	[REDACTED]	09:31:21
20	[REDACTED]	09:31:22
21	[REDACTED]	09:31:23
22	[REDACTED]	09:31:25
23	[REDACTED]	09:31:25
24	[REDACTED]	09:31:27
25	Q I'm sorry. I'm just confirming that he	09:31:28

Transcript of Gerold Mosher
Conducted on February 8, 2022

30

1	continues as your supervisor today?	09:31:30
2	[REDACTED]	09:31:34
3	[REDACTED]	09:31:34
4	A Yes.	09:31:35
5	BY MR. BARRY:	09:31:44
6	[REDACTED]	09:31:44
7	[REDACTED]	09:31:46
8	[REDACTED]	09:31:49
9	[REDACTED]	09:31:53
10	Once you've been given this request, again	09:31:53
11	typically, what would be your next step as a	09:31:56
12	formulator?	09:31:59
13	[REDACTED]	09:32:03
14	[REDACTED]	09:32:04
15	[REDACTED]	09:32:15
16	A I would assess the known parameters,	09:32:15
17	physical chemical parameters of the active drug.	09:32:18
18	I would do literature searches to the extent I	09:32:21
19	could understand what publications are out there	09:32:31
20	as far as the ability to analyze this compound and	09:32:34
21	if there's any data available relative to its	09:32:39
22	susceptibility to acid degradation, base	09:32:44
23	degradation, photodegradation, oxidation, other	09:32:50
24	pathways of degradation.	09:32:55
25	[REDACTED]	09:33:04

Transcript of Gerold Mosher
Conducted on February 8, 2022

31

1	[REDACTED]	09:33:06
2	[REDACTED]	09:33:12
3	[REDACTED]	09:33:14
4	[REDACTED]	09:33:15
5	[REDACTED]	09:33:16
6	[REDACTED]	09:33:17
7	[REDACTED]	09:33:18
8	[REDACTED]	09:33:20
9	[REDACTED]	09:33:22
10	[REDACTED]	09:33:25
11	[REDACTED]	09:33:32
12	[REDACTED]	09:33:34
13	[REDACTED]	09:33:35
14	[REDACTED]	09:33:38
15	[REDACTED]	09:33:46
16	[REDACTED]	09:33:47
17	[REDACTED]	09:33:49
18	[REDACTED]	09:33:51
19	Q I'm trying to I guess I'm wondering	09:33:52
20	whether in that preliminary process when you're	09:33:55
21	learning about the drug product, the process that	09:33:58
22	you just described, would that involve laboratory	09:34:06
23	work generally or is that typically first	09:34:08
24	document based research?	09:34:11
25	[REDACTED]	09:34:13

Transcript of Gerold Mosher
Conducted on February 8, 2022

32

1	[REDACTED]	09:34:16
2	[REDACTED]	09:34:22
3	A First activities would be literature	09:34:22
4	review.	09:34:25
5	[REDACTED]	09:34:31
6	[REDACTED]	09:34:34
7	[REDACTED]	09:34:38
8	[REDACTED]	09:34:46
9	[REDACTED]	09:34:47
10	[REDACTED]	09:34:49
11	[REDACTED]	09:34:53
12	[REDACTED]	09:34:54
13	[REDACTED]	09:35:00
14	[REDACTED]	09:35:01
15	[REDACTED]	09:35:08
16	[REDACTED]	09:35:14
17	[REDACTED]	09:35:15
18	[REDACTED]	09:35:22
19	[REDACTED]	09:35:24
20	[REDACTED]	09:35:25
21	[REDACTED]	09:35:33
22	[REDACTED]	09:35:33
23	[REDACTED]	09:35:34
24	[REDACTED]	09:35:37
25	[REDACTED]	09:35:43

Transcript of Gerold Mosher
Conducted on February 8, 2022

33

1	[REDACTED]	09:35:48
2	[REDACTED]	09:35:48
3	[REDACTED]	09:35:53
4	[REDACTED]	09:35:55
5	[REDACTED]	09:36:01
6	[REDACTED]	09:36:06
7	[REDACTED]	09:36:11
8	[REDACTED]	09:36:14
9	[REDACTED]	09:36:16
10	[REDACTED]	09:36:21
11	[REDACTED]	09:36:22
12	[REDACTED]	09:36:25
13	[REDACTED]	09:36:35
14	[REDACTED]	09:36:45
15	[REDACTED]	09:36:49
16	[REDACTED]	09:36:57
17	[REDACTED]	09:37:02
18	So can you tell me, why does pKa	09:37:07
19	that relevant to the buffer selection?	09:37:12
20	[REDACTED]	09:37:14
21	[REDACTED]	09:37:17
22	[REDACTED]	09:37:22
23	A The ability of a particular buffer species	09:37:22
24	to function at its optimum is dependent upon	09:37:25
25	whether the pH of the environment is reasonably	09:37:33

Transcript of Gerold Mosher
Conducted on February 8, 2022

34

1	close to the pKa of that buffering system or that	09:37:38
2	buffer molecule.	09:37:40
3	BY MR. BARRY:	09:38:08
4	Q So you want the pKa I'm sorry. I want	09:38:08
5	to try to understand your question.	09:38:10
6	You're looking to match, I guess, the pKa	09:38:13
7	with the pH?	09:38:19
8	[REDACTED]	09:38:22
9	[REDACTED]	09:38:27
10	[REDACTED]	09:38:29
11	[REDACTED]	09:38:34
12	A A buffer is most efficient if it is used	09:38:34
13	in a formulation that has a pH approximating one	09:38:41
14	or more of the pKas of that buffer species.	09:38:46
15	[REDACTED]	09:38:49
16	[REDACTED]	09:38:52
17	[REDACTED]	09:38:55
18	[REDACTED]	09:38:55
19	Q You would need to know the pKa of the	09:38:56
20	active ingredient and you would also need to know	09:39:02
21	the pKa of the buffer species; is that correct?	09:39:05
22	[REDACTED]	09:39:08
23	[REDACTED]	09:39:16
24	[REDACTED]	09:39:16
25	A Yes.	09:39:17

Transcript of Gerold Mosher
Conducted on February 8, 2022

35

1	BY MR. BARRY:	09:39:17
2	Q Are the pKas for all buffer species	09:39:18
3	publicized?	09:39:21
4	[REDACTED]	09:39:23
5	[REDACTED]	09:39:25
6	[REDACTED]	09:39:27
7	[REDACTED]	09:39:32
8	A Typically, one can find the pKas of most	09:39:33
9	buffer species in the literature.	09:39:38
10	BY MR. BARRY:	09:39:43
11	Q Was that true prior to 2015?	09:39:44
12	[REDACTED]	09:39:46
13	[REDACTED]	09:39:47
14	[REDACTED]	09:39:50
15	A Yes.	09:39:51
16	[REDACTED]	09:39:51
17	[REDACTED]	09:39:59
18	[REDACTED]	09:40:12
19	[REDACTED]	09:40:15
20	[REDACTED]	09:40:17
21	[REDACTED]	09:40:20
22	[REDACTED]	09:40:23
23	[REDACTED]	09:40:26
24	[REDACTED]	09:40:32
25	[REDACTED]	09:40:37

Transcript of Gerold Mosher
Conducted on February 8, 2022

57

1	[REDACTED]	10:08:18
2	[REDACTED]	
3	A The organoleptic properties of the	10:08:22
4	formulation are always tested and evaluated.	10:08:24
5	[REDACTED]	10:08:40
6	Q Are they always tested and evaluated over	10:08:40
7	time the way that chemical stability is tested?	10:08:44
8	[REDACTED]	10:08:46
9	[REDACTED]	10:08:48
10	[REDACTED]	10:08:50
11	A Most of them are, yes.	10:08:50
12	[REDACTED]	10:09:15
13	Q In your experience, what has been the most	10:09:15
14	common buffer system that you've used?	10:09:17
15	[REDACTED]	10:09:24
16	[REDACTED]	10:09:32
17	[REDACTED]	10:09:32
18	A There is no common one. You would have to	10:09:33
19	be more specific as to the nature of the	10:09:35
20	formulation. Right now I'm using a variety of	10:09:37
21	different buffers.	10:09:39
22	BY MR. BARRY:	10:09:40
23	Q I understand from the process that you	10:09:48
24	would first have established the drug product's	10:09:49
25	pKa and you would have an understanding of the	10:09:54

Transcript of Gerold Mosher
Conducted on February 8, 2022

58

1 buffering, various buffering pictures pKas, and so 10:10:00
2 I guess so if I understand correctly, that 10:10:04
3 would be the initial driver of where you might 10:10:14
4 start with buffer systems; is that fair? 10:10:16

5 [REDACTED] 10:10:23

6 [REDACTED] 10:10:23

7 [REDACTED] 10:10:25

8 A The target pH range of the formulation is 10:10:25

9 the primary driver in the absence of other data. 10:10:28

10 BY MR. BARRY: 10:10:31

11 Q So I want to make sure. So I was 10:10:40

12 imagining a drug formulator receiving instructions 10:10:43

13 and the drug formulator is simply looking the 10:10:45

14 way that you described it, you've got a 10:10:49

15 formulation that somebody wants and they want you 10:10:51

16 to make it. It sounds like it's not a situation 10:10:53

17 where you say, "Oh, I've worked with buffer 10:10:58

18 system A in a variety of things. Let's start 10:11:02

19 there." That's not the process, right? There's 10:11:05

20 more to it? 10:11:09

21 [REDACTED] 10:11:11

22 [REDACTED] 10:11:13

23 [REDACTED] 10:11:18

24 A The experience of the formulator would 10:11:19

25 probably have a number of different buffers 10:11:21

Transcript of Gerold Mosher
Conducted on February 8, 2022

59

1 systems, and when the product requires a
2 particular pH for some reason, sometimes it is for
3 chemical stability, then one would rely on their
4 experience to select buffer system or systems that
5 would be optimal or at least a good place to start
6 with for that particular formulation.

7 [REDACTED]

8 [REDACTED]

9 [REDACTED]

10 [REDACTED]

11 [REDACTED]

12 [REDACTED]

13 [REDACTED]

14 [REDACTED]

15 [REDACTED]

16 Q You agree that buffers are not
17 interchangeable?

18 [REDACTED]

19 [REDACTED]

20 BY THE WITNESS:

21 A I disagree.

22 BY MR. BARRY:

23 Q Can you explain your disagreement.

24 [REDACTED]

25 [REDACTED]

10:11:26

10:11:31

10:11:34

10:11:39

10:11:42

10:11:46

10:11:54

10:11:54

10:11:54

10:11:56

10:11:58

10:11:59

10:12:01

10:12:02

10:12:04

10:12:04

10:12:06

10:12:07

10:12:08

10:12:13

10:12:13

10:12:14

10:12:15

10:12:21

10:12:21

Transcript of Gerold Mosher
Conducted on February 8, 2022

60

1	[REDACTED]	10:12:25
2	A One can select different buffers in any	10:12:26
3	particular formulation that might work equally	10:12:29
4	well.	10:12:33
5	BY MR. BARRY:	10:12:37
6	Q Okay. If I understand correctly, in any	10:12:38
7	given formulation, it may be that more than one	10:12:40
8	buffer will work, right?	10:12:43
9	[REDACTED]	10:12:44
10	[REDACTED]	10:12:47
11	[REDACTED]	
12	A Yes.	10:12:48
13	BY MR. BARRY:	10:12:51
14	Q But it's also true that not every buffer	10:12:51
15	will work, right?	10:12:53
16	[REDACTED]	10:12:55
17	[REDACTED]	10:12:56
18	[REDACTED]	10:13:00
19	[REDACTED]	10:13:01
20	A Yes.	10:13:01
21	[REDACTED]	10:13:02
22	[REDACTED]	10:13:02
23	[REDACTED]	10:13:04
24	[REDACTED]	10:13:04
25	[REDACTED]	10:13:06

Transcript of Gerold Mosher
Conducted on February 8, 2022

61

1	[REDACTED]	10:13:07
2	[REDACTED]	10:13:07
3	[REDACTED]	10:13:21
4	Q And the way that a drug formulator would	10:13:21
5	narrow the options would be by the target pH and	10:13:28
6	the pKa of the buffer, correct?	10:13:33
7	[REDACTED]	10:13:40
8	[REDACTED]	10:13:42
9	[REDACTED]	10:13:49
10	A Typically, yes.	10:13:50
11	[REDACTED]	10:13:54
12	[REDACTED]	10:13:56
13	[REDACTED]	10:13:58
14	[REDACTED]	10:14:01
15	[REDACTED]	10:14:26
16	[REDACTED]	10:25:48
17	[REDACTED]	10:25:51
18	[REDACTED]	10:25:59
19	[REDACTED]	10:26:00
20	[REDACTED]	10:26:02
21	[REDACTED]	10:26:04
22	[REDACTED]	10:26:16
23	[REDACTED]	10:26:18
24	[REDACTED]	
25	[REDACTED]	10:26:23

Transcript of Gerold Mosher
Conducted on February 8, 2022

69

1 BY MR. BARRY:

2 Q Dr. Mosher, what would a formulator how
3 would a formulator use Ora Sweet SF with enalapril
4 to arrive at the same stability profile as the
5 Epaned product?

6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 A I'm not sure how you could get there from
11 Ora Sweet SF. One would need to deformulate and
12 understand the contributions of each and every
13 component and the relative contributions of each
14 those components in the presence of each of the
15 other components in order to truly understand the
16 effects on stability.

17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 [REDACTED]
24 [REDACTED]
25 [REDACTED]

Transcript of Gerold Mosher
Conducted on February 8, 2022

70

1	[REDACTED]	10:39:02
2	[REDACTED]	10:39:04
3	What is the purpose served by the	10:39:05
4	preservative in the Epaned product?	10:39:07
5	[REDACTED]	10:39:12
6	[REDACTED]	10:39:13
7	[REDACTED]	10:39:23
8	A The Epaned oral solution reference listed	10:39:24
9	drug product contains preservatives primarily to	10:39:27
10	support antimicrobial activity.	10:39:33
11	BY MR. BARRY:	10:39:40
12	Q Why is that necessary?	10:39:41
13	[REDACTED]	10:39:43
14	[REDACTED]	10:39:45
15	[REDACTED]	10:39:50
16	A All multi use containers for oral drug	10:39:51
17	products by FDA regulation must contain a	10:39:55
18	antimicrobial preservative or demonstrate that it	10:40:00
19	has those properties over the lifetime of the	10:40:04
20	product.	10:40:06
21	BY MR. BARRY:	10:40:10
22	Q Are preservatives interchangeable?	10:40:10
23	[REDACTED]	10:40:13
24	[REDACTED]	10:40:14
25	[REDACTED]	10:40:16

Transcript of Gerold Mosher
Conducted on February 8, 2022

71

1	BY THE WITNESS:	10:40:22
2	A They can be under some circumstances.	10:40:23
3	BY MR. BARRY:	10:40:25
4	Q Can preservatives affect stability?	10:40:32
5	[REDACTED]	10:40:37
6	[REDACTED]	10:40:38
7	[REDACTED]	10:40:40
8	[REDACTED]	10:40:47
9	Q Under certain circumstances?	10:40:47
10	A Yes, under certain circumstances, yes.	10:40:48
11	Q I know we've identified a lot of different	10:40:54
12	stabilities, but can preservatives affect chemical	10:40:56
13	stability?	10:40:59
14	[REDACTED]	10:40:59
15	[REDACTED]	10:41:01
16	[REDACTED]	10:41:04
17	[REDACTED]	10:41:05
18	A In some instances, yes.	10:41:06
19	BY MR. BARRY:	10:41:08
20	Q Can some preservatives affect physical	10:41:09
21	stability?	10:41:11
22	[REDACTED]	10:41:11
23	[REDACTED]	10:41:12
24	[REDACTED]	10:41:14
25	[REDACTED]	10:41:14

Transcript of Gerold Mosher
Conducted on February 8, 2022

74

1	formulator select preservatives for the oral drug	10:43:28
2	formulations?	10:43:34
3	[REDACTED]	10:43:36
4	[REDACTED]	10:43:37
5	[REDACTED]	10:43:38
6	[REDACTED]	10:43:43
7	A The choice of antimicrobial agent is	10:43:44
8	dependent upon a number of parameters, one being	10:43:47
9	pH, one being the presence of other oxidizing or	10:43:55
10	reducing substances in the formulation, in some	10:43:58
11	cases, whether or not that antimicrobial agent is	10:44:04
12	acceptable for oral administration.	10:44:09
13	BY MR. BARRY:	10:44:23
14	Q Any other criteria?	10:44:23
15	[REDACTED]	10:44:25
16	[REDACTED]	10:44:27
17	[REDACTED]	10:44:28
18	BY THE WITNESS:	10:44:32
19	A One would start looking at a few	10:44:33
20	formulation combinations with various preservative	10:44:35
21	agents and evaluate their performance.	10:44:38
22	[REDACTED]	10:44:45
23	[REDACTED]	10:44:58
24	[REDACTED]	10:45:01
25	Are you responsible for selecting the	10:45:01

Transcript of Gerold Mosher
Conducted on February 8, 2022

75

1	buffers that were ultimately used in the Epaned	10:45:03
2	product?	10:45:09
3	[REDACTED]	10:45:10
4	[REDACTED]	10:45:13
5	A Yes.	10:45:14
6	BY MR. BARRY:	10:45:20
7	Q And were you also responsible for	10:45:21
8	selecting the preservatives or the preservative to	10:45:23
9	be used in the Epaned formulation?	10:45:29
10	[REDACTED]	10:45:30
11	[REDACTED]	10:45:33
12	A Yes.	10:45:34
13	BY MR. BARRY:	10:45:35
14	Q What led you to first of all, I guess,	10:45:35
15	what is the buffer used in Epaned?	10:45:39
16	A The primary buffer system is citric acid.	10:45:46
17	Q What do you mean by "primary"?	10:46:00
18	[REDACTED]	10:46:03
19	BY THE WITNESS:	10:46:10
20	A Any ionizable component of the formulation	10:46:11
21	has a certain buffer capacity, and so one really	10:46:14
22	needs to look at all of the ingredients of the	10:46:18
23	formulation and determine which of those are	10:46:21
24	ionizable and which of those provide buffering	10:46:26
25	capacity.	10:46:29

Transcript of Gerold Mosher
Conducted on February 8, 2022

83

1	[REDACTED]	10:56:26
2	[REDACTED]	10:56:26
3	[REDACTED]	10:56:27
4	[REDACTED]	10:56:30
5	[REDACTED]	10:56:35
6	[REDACTED]	10:56:37
7	[REDACTED]	10:56:41
8	[REDACTED]	10:56:44
9	[REDACTED]	10:56:57
10	[REDACTED]	10:56:57
11	[REDACTED]	10:57:00
12	[REDACTED]	10:57:02
13	[REDACTED]	10:57:07
14	[REDACTED]	10:57:09
15	[REDACTED]	10:57:10
16	[REDACTED]	
17	[REDACTED]	10:57:12
18	[REDACTED]	10:57:15
19	[REDACTED]	10:57:15
20	[REDACTED]	10:57:20
21	[REDACTED]	10:57:23
22	[REDACTED]	10:57:24
23	[REDACTED]	10:57:24
24	[REDACTED]	10:57:28
25	Q What led you to select sodium benzoate as	10:57:28

Transcript of Gerold Mosher
Conducted on February 8, 2022

84

1	a preservative for Epaned?	10:57:33
2	[REDACTED]	10:57:34
3	[REDACTED]	10:57:37
4	A It is very functional in this pH range.	10:57:38
5	BY MR. BARRY:	10:57:40
6	Q Is that based on literature research that	10:57:49
7	you did or independent research?	10:57:51
8	[REDACTED]	10:57:56
9	[REDACTED]	10:57:57
10	A Both.	10:57:58
11	BY MR. BARRY:	10:58:07
12	Q What independent research did you do to	10:58:08
13	determine and to help you identify sodium benzoate	10:58:13
14	as a preservative to Epaned?	10:58:17
15	A I've evaluated the antimicrobial activity	10:58:20
16	of sodium benzoate at various concentrations and	10:58:25
17	various pHs to find those combinations where it	10:58:29
18	passes the antimicrobial efficacy test as required	10:58:31
19	by the FDA.	10:58:35
20	Q Did you experiment with any other	10:58:43
21	preservatives in developing Epaned other than	10:58:46
22	sodium benzoate?	10:58:50
23	[REDACTED]	10:58:51
24	[REDACTED]	10:58:51
25	A Yes. We also looked at a mixture of	10:58:52

Transcript of Gerold Mosher
Conducted on February 8, 2022

85

1	parabens and parabens with benzoate and parabens	10:58:55
2	with sorbic acid.	10:58:59
3	BY MR. BARRY:	10:59:03
4	Q Why did you settle on sodium benzoate?	10:59:04
5	[REDACTED]	10:59:12
6	[REDACTED]	10:59:13
7	A It functions well, and it only requires	10:59:13
8	one component to be added instead of two or three.	10:59:15
9	[REDACTED]	10:59:29
10	[REDACTED]	10:59:30
11	[REDACTED]	10:59:35
12	[REDACTED]	10:59:36
13	[REDACTED]	10:59:37
14	[REDACTED]	10:59:37
15	[REDACTED]	10:59:45
16	[REDACTED]	10:59:46
17	[REDACTED]	11:00:06
18	[REDACTED]	11:00:06
19	[REDACTED]	11:00:08
20	[REDACTED]	11:00:09
21	Q You described the performance of sodium	11:00:10
22	benzoate in the formulation and what I'm trying to	11:00:13
23	understand you said you also tested parabens, and	11:00:16
24	you had said that you settled on sodium benzoate	11:00:19
25	in part because it would only require one	11:00:22

Transcript of Gerold Mosher
Conducted on February 8, 2022

86

1	component, and so I'm trying to understand how	11:00:24
2	does that compare or contrast with paraben?	11:00:27
3	[REDACTED]	11:00:32
4	[REDACTED]	11:00:34
5	[REDACTED]	11:00:40
6	A Parabens can used here. Parabens have	11:00:40
7	variable solubility unless one uses a salt form,	11:00:45
8	so if you choose to use the salt form now you have	11:00:47
9	two components to weigh, increase the potential	11:00:50
10	for error during compounding or during	11:00:53
11	manufacturing. You also have to make sure that	11:00:56
12	both of those species are dissolved. They have	11:00:59
13	very low solubilities. And so I go ahead.	11:01:02
14	[REDACTED]	11:01:11
15	[REDACTED]	11:01:13
16	A So the deference is a single component	11:01:21
17	versus two components as the parabens are	11:01:23
18	typically used in combination such as	11:01:26
19	methyparaben/propylparaben combinations or	
20	methyparaben with benzoate or the parabens with	11:01:31
21	another preservative such as sorbic acid.	11:01:34
22	Q Why not just have one paraben?	11:01:43
23	[REDACTED]	11:01:46
24	[REDACTED]	11:01:49
25	[REDACTED]	11:01:49

Transcript of Gerold Mosher
Conducted on February 8, 2022

87

1 A It's my understanding from the literature 11:01:49
2 that a single paraben does not have the breadth of 11:01:51
3 antimicrobial activity as the combination. 11:01:54

4 [REDACTED] 11:02:00

5 [REDACTED] 11:02:00

6 [REDACTED] 11:02:01

7 [REDACTED] 11:02:02

8 [REDACTED] 11:02:09

9 A It's my understanding from the literature 11:02:10
10 that a single paraben does not have the same 11:02:11
11 antimicrobial activity and spectrum as a 11:02:14
12 combination of parabens. 11:02:16

13 BY MR. BARRY: 11:02:18

14 Q But understanding that one paraben may not 11:02:24
15 have the same antimicrobial activity as multiple 11:02:26
16 parabens, why not use just one paraben in this 11:02:28
17 formulation, the Epaned formulation, instead of 11:02:43
18 sodium benzoate? 11:02:48

19 [REDACTED] 11:02:50

20 [REDACTED] 11:02:51

21 [REDACTED] 11:02:57

22 [REDACTED] 11:02:57

23 A Repeating what I said, if one were to 11:02:58
24 replace sodium benzoate with methylparaben by 11:03:01
25 itself, one would have to at least evaluate to 11:03:05

Transcript of Gerold Mosher
Conducted on February 8, 2022

88

1	make sure that methylparaben by itself is active	11:03:09
2	against all of the microbes that are required for	11:03:13
3	FDA submission.	11:03:17
4	BY MR. BARRY:	11:03:19
5	Q What would your expectation be given your	11:03:20
6	experience?	11:03:22
7	[REDACTED]	11:03:24
8	[REDACTED]	11:03:25
9	[REDACTED]	11:03:35
10	A I would really have to test it to know for	11:03:35
11	sure.	11:03:38
12	BY MR. BARRY:	11:03:38
13	Q How would you go about testing that?	11:03:39
14	[REDACTED]	11:03:40
15	[REDACTED]	11:03:41
16	[REDACTED]	11:03:41
17	A Prepare the formulation at your target	11:03:42
18	levels, at your target pH with all of your	11:03:44
19	ingredients combined and subject it to	11:03:48
20	antimicrobial efficacy testing with microbes.	11:03:51
21	BY MR. BARRY:	11:03:57
22	Q Would you describe that as routine	11:03:58
23	testing?	11:03:59
24	[REDACTED]	11:03:59
25	[REDACTED]	11:04:01

Transcript of Gerold Mosher
Conducted on February 8, 2022

89

1	[REDACTED]	11:04:03
2	[REDACTED]	11:04:09
3	A AET testing is a common test that's in the	11:04:09
4	United States pharmacopeia.	11:04:13
5	BY MR. BARRY:	11:04:17
6	Q You said AET testing. I may have gotten	11:04:18
7	that wrong; is that right, AET?	11:04:21
8	[REDACTED]	11:04:25
9	[REDACTED]	11:04:25
10	A Yes. AET stands for antimicrobial	11:04:26
11	efficacy testing.	11:04:28
12	BY MR. BARRY:	
13	Q You consider the testing that's described	11:04:42
14	in the United States pharmacopeia to be standard?	11:04:44
15	[REDACTED]	11:04:47
16	[REDACTED]	11:04:49
17	[REDACTED]	11:04:51
18	[REDACTED]	11:04:52
19	A This is a commonly used test, yes.	11:04:52
20	[REDACTED]	11:05:11
21	[REDACTED]	11:05:12
22	[REDACTED]	11:05:13
23	[REDACTED]	11:05:20
24	[REDACTED]	11:05:30
25	[REDACTED]	11:05:31

Transcript of Gerold Mosher
Conducted on February 8, 2022

90

1	[REDACTED]	11:05:33
2	[REDACTED]	11:05:33
3	[REDACTED]	11:05:36
4	[REDACTED]	11:05:44
5	[REDACTED]	11:05:52
6	[REDACTED]	11:05:58
7	[REDACTED]	11:06:00
8	[REDACTED]	11:06:00
9	[REDACTED]	11:06:06
10	Q What other buffer systems to the extent	11:06:07
11	you can recall, what other buffer systems did you	11:06:10
12	test?	11:06:12
13	[REDACTED]	11:06:16
14	[REDACTED]	11:06:17
15	A I would need to review data for that. I	11:06:18
16	believe I tested	11:06:23
17	[REDACTED]	11:06:24
18	[REDACTED]	11:06:25
19	[REDACTED]	11:06:27
20	[REDACTED]	11:06:29
21	Q You were about to say sorry.	11:06:33
22	A Yes. I believe we tested several	11:06:37
23	different buffer systems: citrate, citrate	11:06:39
24	phosphate, phosphate by itself, the absence of a	11:06:45
25	buffer, and I believe a number of other buffer	11:06:49

Transcript of Gerold Mosher
Conducted on February 8, 2022

91

1	components. I would have to go back and look at	11:06:57
2	the data.	11:07:00
3	Q Have you formulated drug products using	11:07:29
4	parabens as an antimicrobial agent?	11:07:32
5	[REDACTED]	11:07:34
6	[REDACTED]	11:07:42
7	[REDACTED]	11:07:42
8	A Yes.	11:07:42
9	[REDACTED]	11:07:43
10	Q Have you ever formulated a product using	11:07:43
11	only one paraben?	11:07:49
12	[REDACTED]	11:07:53
13	[REDACTED]	11:07:58
14	[REDACTED]	11:07:58
15	A Not that I recall.	11:07:59
16	[REDACTED]	11:08:01
17	[REDACTED]	11:08:01
18	[REDACTED]	11:08:04
19	[REDACTED]	11:08:08
20	[REDACTED]	11:08:13
21	[REDACTED]	11:08:16
22	[REDACTED]	11:08:20
23	[REDACTED]	11:08:22
24	[REDACTED]	11:08:26
25	[REDACTED]	11:08:27

Transcript of Gerold Mosher
Conducted on February 8, 2022

92

1	[REDACTED]	11:08:28
2	[REDACTED]	11:08:35
3	Q But sitting here, you don't recall ever	11:08:35
4	working on a formulation and using only one	11:08:37
5	paraben as an antimicrobial agent, as a sole	11:08:39
6	antimicrobial agent?	11:08:43
7	[REDACTED]	11:08:47
8	[REDACTED]	11:08:48
9	[REDACTED]	11:08:48
10	A Not that I can remember.	11:08:49
11	[REDACTED]	11:08:50
12	[REDACTED]	11:08:53
13	[REDACTED]	11:08:59
14	[REDACTED]	11:09:02
15	[REDACTED]	11:09:09
16	[REDACTED]	11:09:13
17	[REDACTED]	11:09:14
18	[REDACTED]	11:09:15
19	[REDACTED]	11:09:16
20	[REDACTED]	11:09:17
21	[REDACTED]	11:09:18
22	[REDACTED]	11:09:18
23	[REDACTED]	11:09:24
24	[REDACTED]	11:09:27
25	[REDACTED]	11:09:28

Transcript of Gerold Mosher
Conducted on February 8, 2022

178

1 CERTIFICATE OF COURT REPORTER NOTARY PUBLIC

2
3 I, Theresa A. Vorkapic, Certified
4 Shorthand Reporter No. 084 2589, CSR, RMR, CRR,
5 RPR, and a Notary Public in and for the County of
6 Kane, State of Illinois, the officer before whom
7 the foregoing deposition was taken, do hereby
8 certify that the foregoing transcript is a true
9 and correct record of the testimony given; that
10 said testimony was taken by me and thereafter
11 reduced to typewriting under my direction; that
12 reading and signing was not requested; and that I
13 am neither counsel for, related to, nor employed
14 by any of the parties to this case and have no
15 interest, financial or otherwise, in its outcome.

16 IN WITNESS WHEREOF, I have hereunto set my
17 hand and affixed my notarial seal this 16th day of
18 February, 2022.

19 My commission expires November 6, 2023.

20 

21
22 THERESA A. VORKAPIC

23 NOTARY PUBLIC IN AND FOR ILLINOIS
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US009669008B1

(12) **United States Patent**
Mosher et al.(10) **Patent No.:** **US 9,669,008 B1**(45) **Date of Patent:** **Jun. 6, 2017**(54) **ENALAPRIL FORMULATIONS**(71) Applicant: **Silvergate Pharmaceuticals, Inc.,**
Greenwood Village, CO (US)(72) Inventors: **Gerold L. Mosher**, Kansas City, MO
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MO (US)(73) Assignee: **Silvergate Pharmaceuticals, Inc.,**
Greenwood Village, CO (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) Appl. No.: **15/081,603**(22) Filed: **Mar. 25, 2016****Related U.S. Application Data**(60) Provisional application No. 62/310,198, filed on Mar.
18, 2016.(51) **Int. Cl.**
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A61K 9/00 (2006.01)
A61K 47/26 (2006.01)
A61K 47/12 (2006.01)(52) **U.S. Cl.**
CPC **A61K 31/401** (2013.01); **A61K 9/0053**
(2013.01); **A61K 47/12** (2013.01); **A61K 47/26**
(2013.01)(58) **Field of Classification Search**
None
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner — Jeffrey S Lundgren*Assistant Examiner* — Stephanie Springer(74) *Attorney, Agent, or Firm* — Wilson Sonsini
Goodrich & Rosati(57) **ABSTRACT**

Provided herein are stable enalapril oral liquid formulations. Also provided herein are methods of using enalapril oral liquid formulations for the treatment of certain diseases including hypertension, heart failure and asymptomatic left ventricular dysfunction.

20 Claims, 2 Drawing Sheets

US 9,669,008 B1

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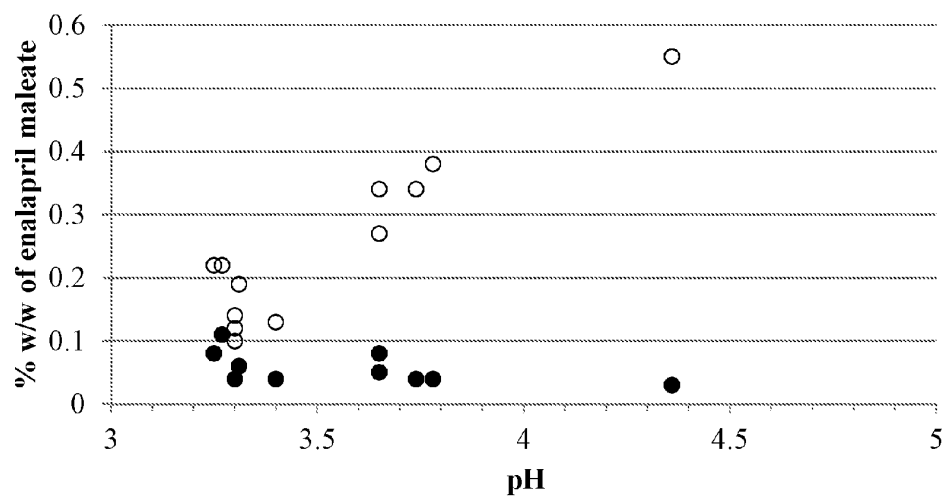
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Sheet 1 of 2

US 9,669,008 B1

FIG. 1

● Enalapril diketopiperazine; ○ Enalaprilat



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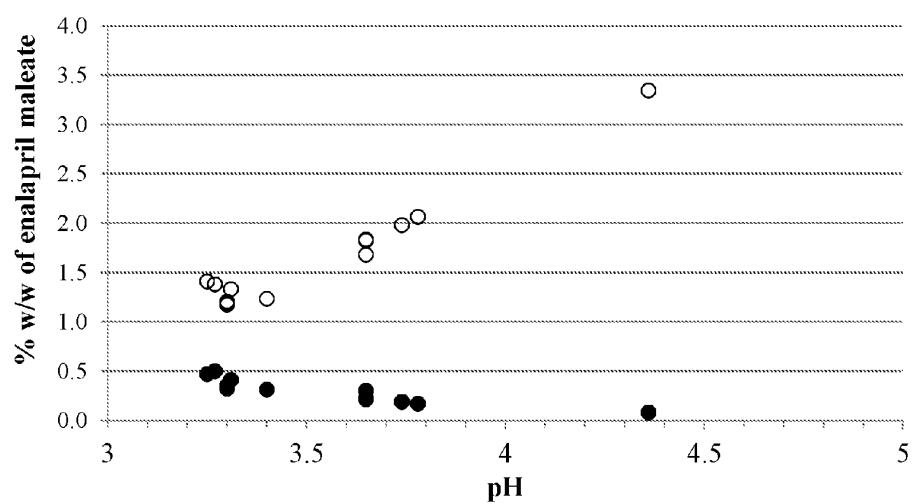
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Sheet 2 of 2

US 9,669,008 B1

FIG. 2

● Enalapril diketopiperazine; ○ Enalaprilat



US 9,669,008 B1

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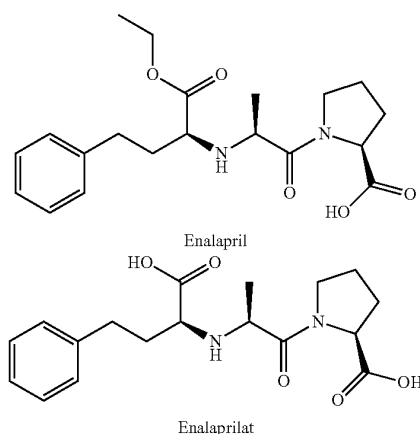
ENALAPRIL FORMULATIONS

BACKGROUND OF THE INVENTION

Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotensin I to angiotensin II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises

2

(i) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the

US 9,669,008 B1

3

formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not

4

contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5°C .

FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature ($19\text{--}22^\circ\text{C}$).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient popu-

US 9,669,008 B1

5

lations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treatment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

6

Enalauril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation

US 9,669,008 B1

7

contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65%

8

w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thau-matin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005—maltodextrin, sorbitol, and fructose combination and Product Code 918.010—water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), Maltisweet™ (maltitol solution, Ingredion), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose T (high fructose corn syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about

US 9,669,008 B1

9

0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids

10

in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89

US 9,669,008 B1

11

mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about

12

0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and Preservative Incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid

US 9,669,008 B1

13

formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

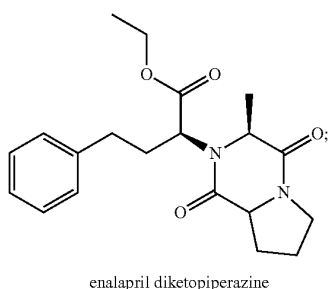
Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

In some embodiments, the oral liquid formulation comprises a buffer.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

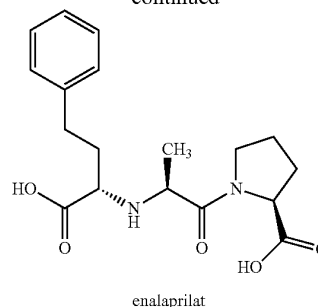
In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



14

-continued



In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml,

US 9,669,008 B1

17

about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40,

18

FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±3° C. In some embodiments, refrigerated condition is about 2° C., about 2.1° C., about 2.2° C., about 2.3° C., about 2.4° C., about 2.5° C., about 2.6° C., about 2.7° C., about 2.8° C., about 2.9° C., about 3° C., about 3.1° C., about 3.2° C., about 3.3° C., about 3.4° C., about 3.5° C., about 3.6° C., about 3.7° C., about 3.8° C., about 3.9° C., about 4° C., about 4.1° C., about 4.2° C., about 4.3° C., about 4.4° C., about 4.5° C., about 4.6° C., about 4.7° C.,

US 9,669,008 B1

19

about 4.8° C., about 4.9° C., about 5° C., about 5.1° C., about 5.2° C., about 5.3° C., about 5.4° C., about 5.5° C., about 5.6° C., about 5.7° C., about 5.8° C., about 5.9° C., about 6° C., about 6.1° C., about 6.2° C., about 6.3° C., about 6.4° C., about 6.5° C., about 6.6° C., about 6.7° C., about 6.8° C., about 6.9° C., about 7° C., about 7.1° C., about 7.2° C., about 7.3° C., about 7.4° C., about 7.5° C., about 7.6° C., about 7.7° C., about 7.8° C., about 7.9° C., or about 8° C. At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g., 25±5° C.; 55±10% RH). In some instances, an accelerated condition is at about 25° C., about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate.

In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a

20

pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents

US 9,669,008 B1

21

include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

22

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of an enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to an enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof; and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing

US 9,669,008 B1

23

can be the same (e.g., 2×10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, an enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include,

24

for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic

US 9,669,008 B1

25

renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76 mg, about 80 mg,

26

about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max}, T_{max}, C_{min}, T_{1/2}) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It

US 9,669,008 B1

27

should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

28

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxymetamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltiazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartin,

US 9,669,008 B1

29

irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

CERTAIN DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms “a” “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

“Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

“Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms

30

“patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of

US 9,669,008 B1

31

the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide					0.075	
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at	Formulation					
	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07

32

TABLE A-2-continued

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at	Formulation					
	A1	A2	A3	A4	A5	A6
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

US 9,669,008 B1

33

TABLE B-1-continued

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours at 60° C.	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		

34

TABLE C-1-continued

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)						
Liquid Formulations						
Storage Formulation						
° C.	Weeks	C1	C2	C3	C4	C5
Diketopiperazine						
5	0	0.03	0.04	0.04	0.02	0.02
	4	0.02	0.03	0.03	0.03	0.02
	8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.02	0.02
	4	0.05	0.09	0.11	0.05	0.04
	8	0.08	0.17	0.19		
	40	0	0.03	0.04	0.02	0.02
	4	0.35	0.91	1.10	0.31	0.21
	8	0.65	1.80	2.05		
Enalaprilat						
5	0	0.18	0.14	0.12	0.13	0.19
	4	0.18	0.15	0.12	0.43	0.53
	8	0.55	0.38	0.34		
	19-23	0	0.18	0.12	0.13	0.19
	4	1.35	0.83	0.80	1.75	2.29
	8	3.34	2.06	1.98		
	40	0	0.18	0.12	0.13	0.19
	4	10.49	6.08	6.11	12.30	16.14
	8	24.37	14.12	14.22		

US 9,669,008 B1

35

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations						
Powder Formulation (grams)						
Component	D1	D2	D3	D4	D5	D6
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)			10.9			
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)			3.00			
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)							
Liquid Formulations							
Storage Formulation							
° C.	Weeks	D1	D2	D3	D4	D5	D6
Diketopiperazine							
5	0	0.04	0.02	0.03	0.03	0.04	0.04
	4	0.07	0.03	0.05	0.05	0.03	

36

TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Liquid Formulations							
Storage Formulation							
° C.	Weeks	D1	D2	D3	D4	D5	D6
19-23	8	0.11	0.06	0.08	0.08	0.05	
	12	0.08	0.04	0.06	0.06		
	26	0.11	0.07	0.09	0.07		
	0	0.04	0.02	0.03	0.03	0.04	0.04
	4	0.27	0.21	0.24	0.16	0.12	0.12
	8	0.50	0.41	0.47	0.30	0.21	0.22
40	12	0.62	0.52	0.58	0.35		
	26	1.39	1.20	1.33	0.76		
	0	0.04	0.02	0.03	0.03	0.04	0.04
	4	2.87	2.32	2.73	1.57	1.21	1.13
	8	5.13	4.42	5.44	2.97	2.23	2.16

TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Liquid Formulations							
Storage Formulation							
° C.	Weeks	D1	D2	D3	D4	D5	D6
55	12	6.86	5.90	6.90	3.91		
	26	13.63	12.18	13.56	7.74		
	Enalaprilat						
	0	0.03	0.02	0.03	0.03	0.13	0.14
	4	0.15	0.12	0.06	0.17	0.13	
	8	0.22	0.19	0.22	0.27	0.34	
60	12	0.20	0.17	0.19	0.22		
	8	0.32	0.30	0.30	0.39		

US 9,669,008 B1

37

TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate) Liquid Formulations Storage Formulation							
° C.	Weeks	D1	D2	D3	D4	D5	D6
19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
	4	0.69	0.66	0.69	0.86	0.74	0.76
	8	1.38	1.33	1.41	1.68	1.83	1.82
	12	1.71	1.68	1.73	2.15		
	26	3.63	3.61	3.59	4.55		
40	0	0.03	0.02	0.03	0.03	0.13	0.14
	4	4.76	4.42	4.76	6.45	5.55	5.24
	8	8.95	8.64	9.61	12.94	12.73	12.18
	12	11.01	10.64	11.41	16.16		
	26	17.18	17.11	18.30	27.36		

Example E: Stability of Solution Formulations of Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C. \pm 3° C., at room temperature (19-23° C.) and at 40° C. \pm 2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate) Storage Formulation							
° C.	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine							
5	0	0.01	0.01	0.01	0.01	0.01	0.01
	4	0.04	0.04	0.05	0.04	0.03	0.03
	8	0.04	0.04	0.04	0.04	0.03	0.03
	12	0.05	0.05	0.04	0.05	0.04	0.04
	26	0.07	0.06	0.05	0.06	0.05	0.05
19-23	52					0.15	0.14
	62	0.18	0.18	0.16	0.14		
	0	0.01	0.01	0.01	0.01	0.01	0.01
	4	0.22	0.23	0.21	0.20	0.16	0.15
	8	0.35	0.35	0.32	0.31	0.29	0.28
40	12	0.58	0.59	0.53	0.51	0.48	0.45
	26	1.10	1.10	1.00	0.95	0.97	0.92
	52					2.30	2.15
	62	3.02	3.04	2.75	2.64		
	4	0.01	0.01	0.01	0.01	0.01	0.01
		2.65	2.71	2.60	2.42	1.76	1.68

38

TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate) Storage Formulation							
° C.	Weeks	E1	E2	E3	E4	E5	E6
5	8	4.02	3.99	3.99	3.62	3.37	3.13
	12	6.72	6.42	6.47	6.00	5.53	5.29
		Enalaprilat					
	5	0	0.00	0.00	0.01	0.00	0.00
	4	0.07	0.09	0.10	0.11	0.07	0.08
10	8	0.12	0.14	0.10	0.13	0.09	0.08
	12	0.16	0.15	0.15	0.17	0.14	0.11
	26	0.31	0.30	0.29	0.31	0.27	0.24
	52					0.54	0.46
	62	0.75	0.75	0.74	0.71		
15	0	0.00	0.00	0.01	0.02	0.00	0.00
	4	0.65	0.65	0.68	0.70	0.50	0.46
	8	1.17	1.19	1.20	1.23	1.03	0.95
	12	1.67	1.69	1.72	1.80	1.30	1.21
	26	3.36	3.38	3.42	3.57	3.07	2.90
20	52					6.32	5.88
	62	7.99	8.02	8.04	8.57		
	0	0.00	0.00	0.01	0.02	0.00	0.00
	4	4.85	4.93	5.19	5.42	3.33	3.25
	8	8.08	8.06	8.56	9.01	6.65	6.35
25	12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. 1 (5°C \pm 3° C.) and FIG. 2 (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
Formulation					
	G1	G2	G3	G4	GS
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	

US 9,669,008 B1

39

TABLE G-1-continued

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of
10 mg Enalapril Maleate Oral Solution vs. 10 mg
Epaned® Powder for Oral Solution (Reconstituted)
Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for

40

the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_{max} were approximately 115% and 109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A stable oral liquid formulation, comprising:

- (i) about 1 mg/mL enalapril maleate;
- (ii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate;
- (iii) about 1 mg/mL of a preservative that is sodium benzoate; and
- (iv) water;

wherein the pH of the formulation is less than about 3.5; and

wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months;

wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

2. The formulation of claim 1, further comprising a flavoring agent.

3. The formulation of claim 1, wherein the pH is between about 3 and about 3.5.

4. The formulation of claim 3, wherein the pH is about 3.3.

5. The formulation of claim 1, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.

6. The formulation of claim 5, wherein the citrate concentration in the buffer is about 10 mM.

7. The formulation of claim 1, wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 18 months.

8. The formulation of claim 1, wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 24 months.

9. The formulation of claim 1, wherein the formulation does not contain mannitol.

US 9,669,008 B1

41

10. The formulation of claim 1, wherein the formulation does not contain silicon dioxide.

11. A stable oral liquid formulation, comprising:

- (i) about 19.3% (w/w of solids) enalapril maleate;
- (ii) a buffer comprising about 35.2% (w/w of solids) citric acid and about 2.9% (w/w of solids) sodium citrate dihydrate;
- (iii) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and
- (iv) water;

wherein the pH of the formulation is less than about 3.5; and

wherein the formulation is stable at about $5\pm 3^{\circ}$ C. for at least 12 months;

wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

12. The formulation of claim 11, further comprising a flavoring agent.

13. The formulation of claim 11, wherein the pH is between about 3 and about 3.5.

14. The formulation of claim 13, wherein the pH is about 3.3.

15. The formulation of claim 11, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.

16. The formulation of claim 15, wherein the citrate concentration in the buffer is about 10 mM.

42

17. The formulation of claim 11, wherein the formulation is stable at about $5\pm 3^{\circ}$ C. for at least 24 months.

18. A stable oral liquid formulation, consisting essentially of:

- (i) about 1 mg/ml enalapril maleate;
- (ii) about 0.70 mg/ml of a sweetener that is sucralose;
- (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate;
- (iv) about 1 mg/ml of a preservative that is sodium benzoate;
- (v) a flavoring agent; and
- (vi) water;

wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid if needed; and

wherein the formulation is stable at about $5\pm 3^{\circ}$ C. for at least 12 months;

wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

19. The stable oral liquid formulation of claim 1, further comprising about 0.70 mg/ml of a sweetener that is sucralose.

20. The stable oral liquid formulation of claim 11, further comprising about 13.5% (w/w of solids) of a sweetener that is sucralose.

* * * * *

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August 29, 2022

The Honorable Mitchell S. Goldberg
United States District Court
for the Eastern District of Pennsylvania
James A. Byrne U.S. Courthouse
601 Market Street – Room 7614
Philadelphia, PA 19106-1797

**CONFIDENTIAL –
FILED UNDER SEAL**

Re: Azurity Pharmaceuticals, Inc. v. Alkem Laboratories Ltd.,
C.A. No. 19-2100 (MSG) (D. Del.)

Dear Judge Goldberg:

Plaintiff Azurity Pharmaceuticals, Inc. (“Azurity”), writes to update the Court regarding the narrowed list of defenses that remain in the case. To avoid surprise in post-trial briefing, the Court ordered Defendant Alkem Laboratories, Ltd. (“Alkem”) to tell Azurity “[h]ere are the defenses we’re pressing and here are the ones we’re not” in advance of the deadline to file post-trial briefs on September 15, 2022. Tr. 565:17-566:13. The parties have exchanged correspondence on this issue.

Alkem withdrew its only noninfringement defense to U.S. Patent No. 10,786,482. When Azurity requested confirmation that Alkem would rely solely on invalidity defenses with respect to the ’482 patent, Alkem insisted that it continues to contest that Azurity has not carried its burden to prove infringement but declined to articulate any purported basis for doing so. Despite multiple attempts, Alkem has refused to share any detail regarding this unidentified noninfringement defense. The parties’ written correspondence is attached to this letter (Ex. A).

As things stand, Azurity is unaware of any remaining noninfringement defense to the ’482 patent. Alkem offered no testimony regarding noninfringement of the ’482 patent. Tr. 204:5-8. When the Court specifically asked Alkem during trial whether it had any noninfringement defense to the ’482 patent, Alkem identified only its now-withdrawn defense. Tr. 204:14-206:16. And in the parties’ correspondence, Alkem merely insisted that Azurity had not carried its burden but refused to identify what element or elements of the claims Azurity had not demonstrated were met by Alkem’s ANDA product.

The Honorable Mitchell S. Goldberg
August 29, 2022
Page 2

Under these circumstances Azurity has little choice but to waste the Court's time (and Azurity's time and limited pages for post-trial briefing) by addressing every conceivable detail regarding infringement of the '482 patent in its post-trial brief – none of which is disputed. Further, if Alkem reveals a new noninfringement position (or any other newfound positions) in its post-trial brief, Azurity may need to request additional briefing to respond to arguments it had no reason to know Alkem was making.

We are available to discuss this matter should the Court have any questions.

Respectfully,

/s/ Megan E. Dellinger

Megan E. Dellinger (#5739)

MD/bac
Attachment

cc: All Counsel of Record (via electronic mail; w/attachment)

EXHIBIT A

Tina <thanson@wsgr.com>; Sumner, Evan <esumner@wsgr.com>; Karol, Jody <ikarol@wsgr.com>; Dellinger, Megan E. <mdellinger@morrisnichols.com>; Chard, Beth Ann <BChard@morrisnichols.com>; Robinson, Kathryn <krobinson@wsgr.com>; Apodaca, Arlene <aapodaca@wsgr.com>

Subject: Re: Azurity Pharmaceuticals, Inc. v. Alkem Laboratories Ltd. (U.S.D.C.(D.Del.), C.A. No. 1:19-cv-02100-MSG)

EXT - tkratz@kratzandbarry.com

Hi Jessica,

Thank you for your follow up inquiry. We will update you when we make specific narrowing decisions, but have not completed our process. We can tell you that we will not be making the non-infringement argument based on the incompatibility of parabens with sugars and sugar alcohols.

As a separate issue, we do not agree with or accept your description of our arguments and we also will not engage in any sort of nitpicking description debate.

We will let you know when we have additional information.

Best regards,

Tim

Timothy H. Kratz | Attorney

Kratz & Barry LLP

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This e-mail may contain confidential or privileged information. If you are not the intended recipient, please advise by return e-mail and delete immediately without reading or forwarding to others.

On Aug 24, 2022, at 6:40 PM, Ramsey, Jessica <jramsey@wsgr.com> wrote:

Counsel,

Please provide the courtesy of a response to my below email or let us know your availability for a live discussion tomorrow.

Regards,
Jessica

From: Ramsey, Jessica

Sent: Monday, August 22, 2022 2:14 PM

To: Touhey Myer <tmyer@kratzandbarry.com>; Timothy Kratz <tkratz@kratzandbarry.com>; George Barry <gbarry@kratzandbarry.com>; Michael Hogan <mhogan@kratzandbarry.com>; Sanaa Hooda <shooda@kratzandbarry.com>; Rachael Covington <rcovington@kratzandbarry.com>

Cc: Devine, Wendy <wdevine@wsgr.com>; Kong, T.O. <TKong@wsgr.com>; Hanson, Tina

<thanson@wsgr.com>; Sumner, Evan <esumner@wsgr.com>; Karol, Jody <jkarol@wsgr.com>; Dellinger, Megan E. <mdellinger@morrisnichols.com>; Chard, Beth Ann <BChard@morrisnichols.com>; Robinson, Kathryn <krobinson@wsgr.com>; Apodaca, Arlene <aapodaca@wsgr.com>

Subject: Azurity Pharmaceuticals, Inc. v. Alkem Laboratories Ltd. (U.S.D.C.(D.Del.), C.A. No. 1:19-cv-02100-MSG)

Counsel,

Pursuant to the Court's order on August 18, the post-trial briefs are due on September 15. (Trial Tr. 566:13-18). As also ordered by the Court, please immediately identify with specificity the defenses Alkem will brief. (Trial Tr. 563:11-564:7).

The list of potential remaining defenses is as follows:

1. Non-infringement of all asserted claims due to disavowal of any combination of parabens and sugars or sugar alcohols;
2. Non-infringement of the asserted claims of the '621 patent due to the potential use of NaOH and HCl during Alkem's manufacturing process;
3. Invalidity of all asserted claims due to improper identification of David Miles as an inventor;
4. invalidity of all asserted claims due to obviousness, the *asserted* prior art pieces now being limited to the '747 patent, Allen, Epaned Insert, Sosnowska, and Nahata with reliance on a POSA's skill and knowledge in light of de Villiers;
5. Invalidity of all asserted claims due to failure to meet the written description requirement arising from absence from the specification of 12-month stability data for a formulation that includes a paraben or a mixture of parabens;
6. Invalidity of all asserted claims due to failure to meet the enablement arising from the absence from the specification of 12-month stability data for a formulation that includes a paraben or a mixture of parabens; and
7. Invalidity of the asserted claims of the '621 patent due to indefiniteness of the term "stable."

Alkem previously dropped its indefiniteness defense arising from the term "buffer." Trial Tr. 474:6-12.

Regards,
Jessica

**WILSON
SONSINI**

Jessica Ramsey (she/her) | Wilson Sonsini Goodrich & Rosati

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30 August 2022

Via CM/ECF (CONFIDENTIAL – FILED UNDER SEAL)

The Honorable Mitchell S. Goldberg
Judge, United States District Court
for the Eastern District of Pennsylvania
James A. Byrne U.S. Courthouse
601 Market Street, Room 17614
Philadelphia, PA 19106-1797

**Re: Azurity Pharmaceuticals, Inc. v. Alkem Laboratories Ltd.
U.S.D.C.(D.Del.)
C.A. No. 1:19-cv-02100-MSG**

Dear Judge Goldberg,

Defendant Alkem Laboratories Ltd. (“Alkem”), writes in response to Plaintiff Azurity Pharmaceuticals, Inc.’s (“Azurity”) letter to your honor dated August 29, 2022, filed under seal at D.I. 189. Alkem had hoped to avoid further burdening the Court with written correspondence discussing post-trial briefing, but it appears Azurity has made that impossible.

Alkem continues to abide by the Court’s Order made at the conclusion of the trial. The deadline to submit post trial-briefs is over two weeks away, and during that time, Alkem will continue to update Azurity regarding any defenses it will not be asserting in its post-trial brief. The email correspondence between counsel submitted as Exhibit A to Azurity’s August 29, 2022 letter speaks for itself, confirming Alkem is acting in good faith and following the Court’s Order, notifying Azurity of any dropped defenses.

Regarding infringement of the ’482 patent, it remains Azurity’s burden to prove their case. It was Azurity’s decision to assert the ’482 patent against Alkem, and it remains Alkem’s position that Azurity did not meet its burden. We do not understand Azurity briefing their infringement case to be a waste of the Court’s time, as it is their burden to do so based on the claims they asserted against Alkem.

The Honorable Mitchell S. Goldberg

30 August 2022

Page 2

Counsel for Alkem remains available at the Court's convenience to discuss this matter further.

Respectfully yours,

A handwritten signature in black ink, consisting of a large, stylized capital 'R' followed by a series of connected loops and a long horizontal stroke extending to the right.

R TOUHEY MYER (#5939)

RTM/rec

cc: All Counsel of Record (*via CM/ECF and E-mail*)

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

AZURITY PHARMACEUTICALS, INC.,

Plaintiff,

v.

ALKEM LABORATORIES LTD.,

Defendant.

Civil Action

No. 19-cv-2100

ORDER

AND NOW, this 2nd day of September, 2022, upon consideration of letters filed by the parties (ECF Nos. 189 & 190), it is hereby **ORDERED** that Plaintiff's request to direct Defendant to further narrow its noninfringement position is **DENIED**.¹

BY THE COURT:

/s/ Mitchell S. Goldberg
MITCHELL S. GOLDBERG, J.

¹ Because a briefing schedule has been issued, the Court does not wish to receive letters addressing the merits of claims or defenses in advance of the briefing.